Ticagrelor for the Treatment of Acute Coronary Syndromes

This shared care agreement outlines the way in which the responsibilities for managing the prescribing of ticagrelor 90 mg tablets for the treatment of acute coronary syndromes can be shared between the Secondary Care Specialist and the General Practitioner.

The National Institute for Health and Care Excellence (NICE) recommends ticagrelor combined with low-dose aspirin for up to a year as a possible treatment for some people with acute coronary syndromes.\(^1\)

**Indication:**

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).\(^2\)

**Dose & Administration:**

Ticagrelor treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment is recommended for up to 12 months unless discontinuation of ticagrelor is clinically indicated. Clinical experience beyond using the drug beyond 12 months is limited and the recommendation is that the drug should be stopped at this point.

**Adverse Effects:**

The most commonly reported adverse effects are dyspnoea, haemorrhage and bruising; less commonly nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, gastritis, dizziness, headache, rash and pruritus; rarely constipation, paraesthesia, confusion, hyperuricaemia, raised serum creatinine and vertigo.

Ticagrelor can commonly cause dyspnoea. In clinical trials most reported symptoms of dyspnoea were mild to moderate in intensity, and most were reported as a single episode early after starting treatment. About 1 in 3 episodes of dyspnoea resolved within 7 days. Patients more likely to report dyspnoea are those with congestive heart failure, COPD, asthma and the elderly. It should be noted that these patients were not excluded from the clinical trial. Ticagrelor does not affect lung function tests. Dyspnoea includes the terms dyspnoea exertional, dyspnoea at rest, and nocturnal dyspnoea. If there are concerns about dyspnoea with ticagrelor that persists beyond 10 days after starting treatment with no identifiable cause GPs should consider discussing this with the patient's consultant.

**Contraindications:**

Contraindications:

- Hypersensitivity to ticagrelor or to any of the excipients included with the medicinal form.
- Active pathological bleeding.
- History of intracranial haemorrhage.
- Moderate to severe hepatic impairment.
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor.

Special warnings/precautions:

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Version: 1  
Author: Paul Mills (Principal Pharmacist-CHUFT)  
Reviewed by: Dr Kare Tang (Consultant Cardiologist), Sheila Baldwin (Head of Medicines Management, NHS North East Essex Clinical Commissioning Group)  
Approved by: NEEMMC  
Next review date: June 2017
- Ticagrelor is not recommended during pregnancy. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor therapy.

- Ticagrelor is excreted into breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from ticagrelor therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

- The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, ticagrelor should be used with caution in the following patient groups:
  - Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). But see contraindications above
  - Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of ticagrelor dosing.

- If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 7 days prior to surgery.

- Ticagrelor should be used with caution in patients with history of asthma and/or COPD. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped.

- Creatinine levels may increase during treatment with ticagrelor. Renal function should be checked after one month and thereafter according to routine medical practice, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB.

- The use of ticagrelor in patients with uric acid nephropathy is discouraged.

**Drug Interactions:**

The ticagrelor Summary of Product Characteristics gives full details of the drug interactions associated with the treatment.

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. It is also a P-gp substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

Interactions with ticagrelor are listed below (those in red indicates the combinations that should be avoided):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>plasma concentration of ticagrelor possibly increased by atazanavir — manufacturer of ticagrelor advises avoid concomitant use</td>
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<tr>
<td>Carbamazepine</td>
<td>plasma concentration of ticagrelor possibly reduced by carbamazepine</td>
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<tr>
<td>Ciclosporin</td>
<td>plasma concentration of ticagrelor increased by ciclosporin</td>
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<tr>
<td>Citalopram</td>
<td>possible increased risk of bleeding when ticagrelor given with citalopram</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>plasma concentration of ticagrelor possibly increased by clarithromycin — manufacturer of ticagrelor advises avoid concomitant use</td>
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<tr>
<td>Dabigatran</td>
<td>ticagrelor increases plasma concentration of dabigatran</td>
</tr>
<tr>
<td>Digoxin</td>
<td>ticagrelor increases plasma concentration of digoxin</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>plasma concentration of ticagrelor increased by diltiazem</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>ticagrelor possibly increases plasma concentration of ergot alkaloids</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>plasma concentration of ticagrelor possibly increased by erythromycin — Note: Interactions do not apply to small amounts of erythromycin used topically</td>
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<tr>
<td>Fosphenytoin</td>
<td>plasma concentration of ticagrelor possibly reduced by fosphenytoin</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>possible increased risk of bleeding when ticagrelor given with</td>
</tr>
<tr>
<td>Drug</td>
<td>Effect</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Plasma concentration of ticagrelor possibly reduced by phenobarbital</td>
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<tr>
<td>Phenobarbital</td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>Plasma concentration of ticagrelor possibly reduced by phenytoin</td>
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<tr>
<td>Primidone</td>
<td>Plasma concentration of ticagrelor possibly reduced by primidone</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Plasma concentration of ticagrelor reduced by rifampicin</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Plasma concentration of ticagrelor possibly increased by ritonavir —</td>
</tr>
<tr>
<td></td>
<td>manufacturer of ticagrelor advises avoid concomitant use</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Possible increased risk of bleeding when ticagrelor given with sertraline</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Ticagrelor increases plasma concentration of simvastatin (increased risk of toxicity)</td>
</tr>
</tbody>
</table>

**Monitoring Requirements:**

Creatinine levels may increase during treatment with ticagrelor (the mechanism for this effect not being fully elucidated). Renal function should be checked after one month of treatment and thereafter according to routine medical practice, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB.

**Parameters for Intervention:**

Apart from the recommended renal function test at one month post-treatment, there are no specific parameters for intervention in terms of blood tests, therapeutic monitoring, etc. Any possible ticagrelor-related adverse effects must be reported back to the Secondary Care Specialist who will then make a decision as to the clinical appropriateness of continuing therapy.

**Shared Care Responsibilities:**

**Secondary Care Specialist**

1. Send a letter to the GP with Shared Care Guidelines requesting shared care for the patient.
2. Initiation of ticagrelor therapy with the correct dose prescribed; providing the patient with an initial 4 weeks supply of medicine.
3. Discuss the benefits and side effects of treatment with the patient.
4. Clearly state to the patient that treatment duration is intended to be for a maximum of 12 months.
5. Report adverse events to the Medicines and Healthcare Products Regulatory Agency (MHRA).
6. Act promptly on any communication from GP colleagues requesting advice and support.
7. Communicate the decision to discontinue therapy prior to the completion of the 12 month treatment period; if on-going therapy is no longer thought to be beneficial.

**Primary Care Practitioner**

1. Submit letter of reply confirming acceptance.
3. Prescribe the drug treatment as described within this document.
4. Continue prescribing ticagrelor (usually after a minimum of 4 weeks therapy); stopping therapy after a 12 month period, from initiation, has elapsed.
5. To undertake any necessary monitoring of the patient, including checking renal function after one month of treatment. Future checks should be carried out in accordance with routine medical practice paying special attention to patients aged ≥ 75 years, patients with moderate/severe renal impairment and those requiring monitoring with regards to concomitant medication.
6. Report to and seek advice from the Secondary Care Specialist on any aspect of patient care that is of concern and may affect treatment.
7. Refer patient to the Specialist if his or her condition deteriorates.
8. Report any ticagrelor-related adverse events to the hospital specialist and MHRA.
9. Ensure that any new medication started is reviewed in terms of interactions with ticagrelor.
10. Stop treatment on the advice of the Secondary Care Specialist.
11. Consider adding “to be taken until …..” on future ticagrelor prescriptions.

**Patient (and if appropriate, the carer):**

1. Report to the Secondary Care Specialist or GP if he or she does not have a clear understanding of the prescribed treatment.
2. Share any concerns in relation to treatment with ticagrelor.
3. Report any adverse effects to the Secondary Care Specialist or GP whilst taking ticagrelor therapy.

**Contact Numbers for Advice and Support:**

Colchester Hospital University NHS Foundation Trust (01206) 747474 (Switchboard)

**Consultant Cardiologists:**

Dr Kare Tang (01206) 742219 kare.tang@colchesterhospital.nhs.uk

Dr Alan Harkness (01206) 742626 alan.harkness@colchesterhospital.nhs.uk

**CHUFT Pharmacy Department**

(01206) 742355

**CHUFT Medicines Information Help Line:**

(01206) 742161

**References**

(1) Ticagrelor for the treatment of Acute Coronary Syndromes, October 2011
https://www.nice.org.uk/guidance/ta236

(2) Summary of Product Characteristics – Brilique® (ticagrelor) 90mg film-coated tablets. Astra Zeneca UK Limited.
https://www.medicines.org.uk/emc/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/

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**Section A (to be completed by Secondary Care Specialist):**

Version: 1
Author: Paul Mills (Principal Pharmacist-CHUFT)
Reviewed by: Dr Kare Tang (Consultant Cardiologist), Sheila Baldwin (Head of Medicines Management, NHS North East Essex Clinical Commissioning Group)
Approved by: NEEMMC  June 2015
Next review date: June 2017
**Background:**

**Medications:**

Dear GP,
See attached clinic letter. Please can you sign and return (using the above fax number) to indicate you are in agreement with the Shared Care Guidelines.

Yours sincerely,

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**Section B (to be completed by General Practitioner):**

The above patient (with associated ticagrelor treatment) has been accepted into our monitoring service.

<table>
<thead>
<tr>
<th>Accepting GP Name:</th>
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<tbody>
<tr>
<td>Accepting GP Signature:</td>
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<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>

Practice Stamp: