HERPC

Hull & East Riding Prescribing Committee

Ticagrelor for preventing atherothrombotic events after myocardial infarction

1. BACKGROUND

NICE Technology appraisal guidance (TA420) published in December 2016 recommends a dose of Ticagrelor 60mg TWICE a day in combination with low dose aspirin as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and at high risk of a further event.

Risk of atherothrombotic events:

The PEGASUS-TIMI 54 trial was the trial that formed the basis of the submission to NICE. In this trial, patients had a history of MI, occurring 12 and 36 months before entry, were at least 50 years of age and had at least one of the following additional high-risk factors:

- Age 65 or older
- Diabetes mellitus requiring medication
- A second prior spontaneous MI
- Multivessel coronary artery disease
- Chronic renal function (defined as creatine clearance of <60mls/min)

The hazard ratio for 60mg of ticagrelor vs. placebo, 0.84%; (95% confidence interval (CI), 0.74 to 0.95); P=0.004 reduction rates of cardiovascular death, myocardial infarction, and stroke through 3 years.

2. INDICATION

Consider prescribing Ticagrelor 60mg twice a day for selected patients with a history of MI within 2 years who are at high risk of further events:

- Without interruption as continuation therapy after the initial 1 year treatment with Ticagrelor 90mg twice a day or alternative treatment (clopidogrel or prasugrel)
- Initiated up to 2 years from the MI, or within 1 year of stopping Ticagrelor 90mg twice a day or alternative treatment (clopidogrel or prasugrel)
- One or more of the above high-risk factors should be taken into consideration when assessing the risks of future events

3. Dose

- **Ticagrelor 60mg TWICE a DAY for up to 3 years** in combination with **aspirin 75mg once a day lifelong**
- **Started without interruption of at least 1 year of ticagrelor 90mg twice a day**

4. DRUG INTERACTIONS

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP4A4, also a P-glycoprotein (P-gp) substrate and a weak P-glycoprotein inhibitor and may increase the exposure of P-glycoprotein substrates.

Selected drug interactions (See BNF/SPC for a full up to date list)

Drug Interactions	
Strong CYP3A4 inhibitors: Ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir	Contra-indicated – significant increase in ticagrelor levels

Moderate CYP3A4 inhibitors: Erythromycin, fluconazole, diltiazem	Caution – increase or possible increase in ticagrelor levels
NSAID's and SSRI's (paroxetine, sertraline, citalopram)	Caution - may increase the risk of bleeding
CYP3A inducers: Rifampicin, phenytoin, carbamazepine and phenobarbital	Discourage – may lead to a decrease in exposure and efficacy of ticagrelor
P-glycoprotein and CYP3A inhibitors: Cyclosporin, verapamil and quinidine	Caution - may increase ticagrelor exposure
P-glycoprotein substrates: Digoxin	Digoxin levels maybe increased – monitor plasma digoxin levels advised
CYP3A4 substrates with narrow therapeutic index: i.e. ergot alkaloids	Not recommended – ticagrelor may increase the levels of ergot alkaloids
Drugs metabolised by CYP3A4: Simvastatin	Greater than 40mg is not recommended
Warfarin and new oral anticoagulant agents	Co-prescribing with ticagrelor increases the risk of bleeding – use with caution or avoid

5. CONTRAINDICATIONS AND CAUTIONS

Contra-indications

Ticagrelor is contra-indicated in the following situations:

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

Cautions

Ticagrelor should be used with caution in the following patient groups: -

- Increased risk of bleeding
- Patients with a tendency to bleed (e.g. due to trauma, recent surgery, coagulation disorders, active or recent GI bleeding)
- Patients on concomitant administration of medications 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
- Antifibrinolytic therapy (tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.
- Elective surgery – discontinue ticagrelor 5 days prior to surgery
- Prior ischaemic stroke – in PEGASUS patients with a history of MI with prior ischaemic stroke were not include in the trial, treatment is not recommended with ticagrelor 60mg in this patient group
- Patients at risk of bradycardia
- Asthma/COPD: If a patient, particularly those with pre-existing asthma/COPD reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped and replaced with an alternative agent (clopidogrel, prasugrel).
- Renal impairment: Creatinine levels may increase during treatment with ticagrelor. Renal function should be checked at baseline, after one month and then as clinically indicated, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).
- Ticagrelor may increase the risk of hyperuricaemia. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. Ticagrelor is not recommended in patients with uric acid nephropathy.
- Co-administration of ticagrelor with high maintenance dose aspirin >300mg is not recommended

- Premature discontinuation should be avoided could result in an increased risk of cardiovascular death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

- Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor treatment
- Pregnancy - Ticagrelor is not recommended during pregnancy
- Breast-feeding - excretion of ticagrelor and its active metabolite has been shown in animal milk in pharmacodynamics/toxicological data. Therefore risk to newborns/infants cannot be excluded.

6. ADVERSE EFFECTS

The most commonly reported adverse reactions (≥ 1/10) are blood disorder bleedings, hyperuricaemia, and dyspnoea

7. INFORMATION TO PATIENT

Patients should be advised on common side-effects

- Bruising
- Dyspnoea

All patients should be counselled on the duration of treatment
Ticagrelor tablets are taken with or without food
Lapses in treatment and missed doses avoided. If a missed dose occurs, take one tablet at the next scheduled time (don't double the dose)
Avoid NSAIDs as increased bleeding risk
Patients should be advised to inform physician and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medications is taken
Ticagrelor has no specific storage requirements and is suitable for compliance aids

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

APPROVAL PROCESS

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