

## Additional Notes for Chapter 8 – Central Nervous System

### 8.1 Cytotoxics

The following are common side effects that may affect patients taking cytotoxic drugs; for specific side effects refer to links below and/or individual SPCs [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc) and the [pharmacy Guidelines for the safe use of oral anti-cancer medicines](#).

#### Neutropenia

Complications of neutropenia can be life threatening and require urgent investigation and treatment. [Greater Manchester & Cheshire cancer network \(GMCCN\) guidelines](#) provide information for the management of sepsis (including neutropenic sepsis) and for the use of growth factors

Patients undergoing chemotherapy, presenting with bruising, epistaxis, or bleeding, require an urgent full blood count. Patients with bleeding/bruising or those with platelets less than  $10 \times 10^9/L$ , require urgent hospital admission for investigation and platelet support.

#### Anaemia

Patients with symptomatic anaemia and haemoglobin of less than 8.5g/dL require transfusion.

#### Nausea and vomiting

Choice of anti-emetics is determined by the emetogenic potential of the chemotherapy or radiotherapy regimen. See [GMCCN guidelines for the use of anti-emetics](#)

#### Mucositis and mouthcare

Further information is available in the [GMCCN oral care protocol](#).

#### Extravasation injury

See [GMCCN extravasation policy](#).

#### Diarrhoea

See [GMCCN guidelines for the management of chemotherapy induced diarrhoea in adult patients with cancer](#). Diarrhoea is specifically associated with irinotecan and bortezomib. As soon as the first liquid stool occurs patient must increase oral fluid intake and commence loperamide: 4mg stat then 2mg every 2 hours until 12 hours after last liquid stool – max 48 hours due to risk of paralytic ileus.

#### Other toxicities

Cardiotoxicity, nephrotoxicity and pulmonary toxicity are more drug or class-specific, may depend on cumulative drug exposure, the schedule of administration and previous therapy.

Refer to individual SPC ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc)).

## 8.2.4 Other immunomodulating drugs

### Interferon Alfa

Interferon alfa used in certain lymphomas and solid tumours. It is also used in the treatment of chronic hepatitis B and chronic hepatitis C ideally in combination with ribavirin.

Polyethylene glycol-conjugated ('pegylated') derivatives of interferon alfa are available; pegylation increases the persistence of the interferon in the blood. The peginterferons are licensed for the treatment of chronic hepatitis C, ideally in combination with ribavirin. Peginterferon alfa-2a is also licensed for the treatment of chronic hepatitis B.

### BCG bladder installation

BCG (Bacillus Calmette-Guérin) is a live attenuated strain derived from *Mycobacterium bovis*. It is licensed as a bladder instillation for the treatment of primary or recurrent bladder carcinoma and for the prevention of recurrence following transurethral resection.

### Canakinumab

Canakinumab is a beta receptor binding. It is licensed for the treatment of cryopyrin-associated periodic syndrome, including severe forms of familial cold auto-inflammatory syndrome (or familial cold urticaria), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurological cutaneous and articular syndrome). These are rare inherited auto-inflammatory disorders.

Patients should be evaluated for latent and active tuberculosis before starting treatment and monitored for signs and symptoms of tuberculosis during and after treatment

This drug comes under specialist commissioning arrangements for cryopyrin-associated periodic syndrome and the only national treatment centre is the Royal Free London NHS Trust.

### Fingolimod

Fingolimod is an immunomodulating drug licensed for use in patients with highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta or in those with rapidly evolving severe relapsing-remitting multiple sclerosis.

Fingolimod is a RED drug and GPs will not be asked to prescribe it, however they need to be aware of the drug-drug interactions if they have patients receiving it from secondary care.

Fingolimod is not recommended in those patients receiving the following antiarrhythmic or heart-rate-lowering drugs:

- Class Ia antiarrhythmics (eg, quinidine, disopyramide)
- Class III antiarrhythmics (eg, amiodarone, sotalol, dronedarone)
- Class II: Beta blockers
- Heart rate-lowering calcium channel blockers (eg, verapamil, diltiazem or ivabradine)
- Other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
- phenytoin, carbamazepine, oxcarbazepine and eslicarbazepine have potential to cause bradycardia and prescription with fingolimod may require additional cardiac monitoring.

In such patients, treatment with Fingolimod (Gilenya®) should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist is sought prior to initiation of fingolimod treatment.<sup>2</sup>

This advice should include, if appropriate, the possibility to switch any concomitant medicines to treatments that are not anti arrhythmic and do not lower heart rate. If treatment with fingolimod for these patients is considered, monitoring at least overnight following the first dose should be initiated.

Fingolimod is metabolised mainly by CYP4F2, and other enzymes such as CYP3A4 contribute to its metabolism. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin). Fingolimod has not been studied in patients receiving drugs that prolong the QT interval<sup>3</sup>.

**GPs should not, therefore, commence any of the above drugs in patients currently on fingolimod. If any patients receiving fingolimod require any cardiovascular medications they should be referred to cardiology for specialist input and monitoring, or discuss options with the MS Specialist.**

MHRA advice: fingolimod is not recommended for patients at known risk of cardiovascular events. Advice for extended monitoring for those with significant bradycardia or heart block after the first dose ([MHRA DSU May 2012](#)) and for subsequent doses ([MHRA DSU January 2013](#))

## Lenalidomide and thalidomide

Thalidomide is used in combination with melphalan and prednisolone as first-line treatment for untreated multiple myeloma, in patients aged 65 years and over, or for those not eligible for high-dose chemotherapy (for example, patients with significant co-morbidity such as cardiac risk factors). It has immunomodulatory and anti-inflammatory activity.

Lenalidomide is an immunomodulating drug with antineoplastic, anti-angiogenic, and pro-erythropoietic properties. It is licensed, in combination with dexamethasone, for the treatment of multiple myeloma in patients who have received at least one previous therapy.

The most serious side-effects of lenalidomide are venous thromboembolism and severe neutropenia. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis.

For women of child-bearing potential, pregnancy must be excluded before starting treatment (perform pregnancy test on initiation or within 3 days prior to initiation). Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment (oral combined hormonal contraceptives and copper-releasing intrauterine devices not recommended) and men should use condoms during treatment and for at least 1 week after stopping if their partner is pregnant or is of child-bearing potential and not using effective contraception. Women must comply with a pregnancy prevention programme.

For both lenalidomide and thalidomide, patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form, which must be sent to Celgene (manufacturers).

### **Mifamurtide**

Mifamurtide is licensed for high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection, in patients 2 to 30 years of age at initial diagnosis. It is used in combination with chemotherapy.

Patient access scheme available.

### **Natalizumab**

Natalizumab is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination. It is licensed for use in patients with highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta or those with rapidly evolving severe relapsing-remitting multiple sclerosis.

Liver dysfunction reported; advise patients to seek immediate medical attention if symptoms such as jaundice or dark urine develop; discontinue treatment if significant liver injury occurs

Patients should be informed about the risks of progressive multifocal leucoencephalopathy (PML) before starting treatment with natalizumab and again after 2 years; they should be given an alert card which includes information about the symptoms of PML.

Hypersensitivity reactions - patients should be told the importance of uninterrupted dosing, particularly in the early months of treatment (intermittent therapy may increase risk of sensitisation)

### **8.3.4 Hormone Antagonist**

#### **8.3.4.1 Breast Cancer**

##### **Tamoxifen**

Tamoxifen: the cytochrome P450 enzyme, CYP2D6 is the rate-limiting step in the conversion of tamoxifen to its most active metabolite, endoxifen. Some retrospective studies have shown that drugs which inhibit the enzyme activity of CYP2D6 have been shown to increase the relapse rate in patients on adjuvant tamoxifen. Such drugs include two commonly used antidepressants fluoxetine and paroxetine. Where possible, the prescription of moderate / potent CYP2D6 inhibitors with tamoxifen should be avoided. The final decision will be a clinical judgement of risk and benefit.

#### **8.3.4.2 Gonadorelin analogues and gonadotrophin-releasing hormone antagonists**

##### **Goserelin**

Goserelin (Zoladex®) is the only licensed GnRH analogue for use in the treatment of breast cancer. It is also used in IVF and endometrial thinning before intra-uterine surgery

##### **Bicalutamide**

Bicalutamide is the only anti-androgen licensed as a single agent for monotherapy in a patient with locally advanced disease. The dosage of bicalutamide is 150mg once daily as a single agent, or 50mg once daily when given in conjunction with gonadorelin analogue injection therapy. Care should be taken to ensure correct choice of dose.

##### **Cyproterone acetate**

Cyproterone acetate: Direct hepatic toxicity including jaundice, hepatitis and hepatic failure has been reported (usually after several months) in patients treated with cyproterone acetate 200-300 mg daily. Liver function tests should be performed before treatment and whenever symptoms suggestive of hepatotoxicity occur-if confirmed cyproterone should normally be withdrawn. Cyproterone is no longer recommended for long term use.

##### **Degarelix**

Switching from degarelix to other LHRH therapies must only be undertaken following specialist consultation.

### 8.3.4.3 Somatostatin analogues.

#### Octreotide

Octreotide injection is licensed for acromegaly and symptoms associated with carcinoid syndrome and neuroendocrine tumours. It is also used in hospital to manage high output stomas after surgery and in the palliative care setting as a subcutaneous infusion to reduce intestinal secretions and to reduce vomiting due to bowel obstruction (unlicensed use).