SHARED CARE PROTOCOL: VORICONAZOLE (ADULTS)

NHS GREATER GLASGOW AND CLYDE

NB: This document should be read in conjunction with the current Summary of Product Characteristics (SPC)

DRUG AND INDICATION:

Generic drug name:	**Voriconazole**
Formulations:	Film coated tablet containing 50mg or 200mg voriconazole
Intended indication:	Treatment of invasive aspergillosis (respiratory patients only)
Status of medicine or treatment:	Licensed indication for licensed medicine Formulary medicine

RESPONSIBILITIES OF ACUTE CARE/SPECIALIST SERVICE (CONSULTANT):

- Undertake baseline investigations/monitoring and initiate treatment or ask GP to initiate treatment.
- Dose adjustments
- If appropriate, ensure that the patient has an adequate supply of medication (usual minimum of 28 days) until the shared care arrangements are in place

Acute care/specialist service will provide the GP with:

- An initiation letter (which includes diagnosis, relevant clinical information, baseline results, treatment to date, treatment plan, duration of treatment before consultant review)
- Details of outpatient consultations, ideally within 14 days of seeing the patient

Acute care will *(see healthcare professional checklist):*

- Provide the patient with relevant drug information to enable:
  - Informed consent to therapy
  - Understanding of potential side effects and appropriate action
    - Educate patients about avoiding exposure to direct sunlight during treatment with voriconazole and the use of high sun protection factor.
    - Patients should be asked to inform you immediately of the occurrence of sunburn or severe skin reaction following exposure to light or sun.
  - Understanding of the role of monitoring

- Re-check for drug interactions each time a new drug is commenced.
- Provide a Patient Alert Card where appropriate

Healthcare professional checklist and Patient Alert Card available at https://www.gov.uk/drug-safety-update/voriconazole-reminder-of-risk-of-liver-toxicity-phototoxicity-and-squamous-cell-carcinoma

RESPONSIBILITIES OF PRIMARY CARE (GENERAL PRACTITIONER):

- To prescribe in collaboration with the specialist according to this protocol
- Symptoms or results are appropriately actioned, recorded and communicated to acute care when necessary
- Re-check for drug interactions each time a new drug is commenced.

RESPONSIBILITIES OF PATIENT:

- To attend hospital and GP clinic appointments
- Failure to attend appointments will result in medication being stopped.
- To report adverse effects to their specialist or GP
    - In particular, symptoms of phototoxicity such as sunburn.
- To follow advice given about sun exposure, including use of high factor sun protection.
- To carry patient alert card (if given) at all times.
- To tell the acute care physician or general practitioner about any use of over-the-counter or herbal medicine.
- To seek advice from a pharmacist or other healthcare professional before taking any new medicines including over-the-counter and herbal medicines.

ADDITIONAL RESPONSIBILITIES:

- Any serious reaction to an established drug should be reported to the CHM using the yellow card scheme.

CAUTIONS:

- Voriconazole has been associated with QTc interval prolongation. Administer with caution in patients with potentially arrhythmogenic conditions such as; congenital or acquired QT-prolongation, cardiomyopathy (in particular when heart failure present), sinus bradycardia (<50 bpm), existing symptomatic arrhythmias, concomitant medicinal product that is known to prolong QT interval, history of cardiotoxic chemotherapy, uncorrected hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Use with caution in patients at risk of pancreatitis.
- Advise patients to avoid exposure to sunlight while taking voriconazole. Advise patients to wear protective clothing and use sunscreen with a high sun protection factor if in sunlight.
- Long-term treatment (greater than 6 months) may increase the risk of squamous cell carcinoma of the skin. Treatment should be as short as possible and long-term treatment should be considered only if the benefits outweigh the risks.
- Seek specialist dermatologist advice if there are concerns about those patients at increased risk of skin malignancy or a history of skin malignancy. Patients developing new lesions during treatment should be referred urgently to skin cancer services.

CONTRAINDICATIONS:

- Hypersensitivity to the drug or any of the excipients (see SPC for list)
- Co-administration with some drugs is contraindicated, these are listed under Significant Drug Interactions (full details from SPC).

TYPICAL DOSAGE REGIMENS:

<table>
<tr><td>Route of administration:</td><td colspan="3">Oral</td></tr>
<tr><td rowspan="4">Recommended starting dose:</td><td colspan="3">Dosing for adults, adolescents 15 years and over (or aged 12-14 with body weight over 40kg)</td></tr>
<tr><td></td><td>Patients 40kg and above</td><td>Patients less than 40kg</td></tr>
<tr><td>Loading dose regimen
(first 24 hours)</td><td>400mg every 12 hours</td><td>200mg every 12 hours</td></tr>
<tr><td>Maintenance dose regimen
(after first 24 hours)</td><td>200mg twice daily

(can increase to 300mg twice daily if response to treatment is inadequate. Reduce in 50mg steps if patient is unable to tolerate higher dose)</td><td>100mg twice daily

(can increase to 150mg twice daily if response to treatment is inadequate. Reduce in 50mg steps if patient is unable to tolerate higher dose)</td></tr>
<tr><td>Adjunctive treatment regimen:</td><td colspan="3">Nil</td></tr>
<tr><td>Conditions requiring dose adjustment:</td><td colspan="3">In mild to moderate hepatic cirrhosis (Child-Pugh A and B), use the normal initial dose then halve subsequent doses. Voriconazole has not been studied in severe chronic hepatic cirrhosis (Child-Pugh C).</td></tr>
</table>

	No dosage adjustment is required in renal impairment.
Usual response time:	Time to response is variable, dependent on many patient and disease factors.
Duration of treatment	Variable. Treatment duration should be as short as possible and long-term treatment (greater than 6 months) should only be considered if the benefits outweigh the potential risks (see Cautions/Undesirable Effects).

All dose adjustments will be done in acute care unless directions have been specified in a medical letter to the GP

SIGNIFICANT DRUG INTERACTIONS:

Voriconazole has the potential to interact with many medicines. See BNF/SPC for full details of interactions and the stopping/starting of interacting drugs.

Some combinations are **contraindicated** and must not be co-prescribed. **Examples** of drugs that **must be avoided** include:

- Astemizole
- Carbamazepine
- Ergotamine
- Everolimus
- Phenobarbital and long-acting barbiturates
- Pimozide
- Quinidine
- Rifampicin
- Ritonavir
- St John's Wort
- Terfenadine

Voriconazole interacts with a variety of drugs due to inhibition of the cytochrome P450 enzyme system. Some combinations can be prescribed but may require additional monitoring. **Examples** of drugs that require **additional monitoring** or **dose adjustment** include:

- Immunosuppressants (ciclosporin, sirolimus, tacrolimus)
- Warfarin and coumarins
- Opioid analgesics
- Oral contraceptives
- Benzodiazepines
- Efavirenz
- NSAIDs
- Statins
- Omeprazole
- Sulphonylureas
- Methadone
- Phenytoin
- Rifabutin

UNDESIRABLE EFFECTS:

ADR details (where possible indicate if common, rare or serious)	Management of ADR
Liver toxicity Usually occurs within the first 10 days of treatment.	Stop voriconazole if AST or ALT levels become markedly elevated, unless you consider the benefits of voriconazole treatment to outweigh the risk of liver toxicity in that individual. Liver function usually reverts to normal when voriconazole is stopped.
Phototoxicity/squamous cell carcinoma	Refer patients with phototoxic reactions to a dermatologist and consider stopping voriconazole treatment. Seek advice from acute care about discontinuation of treatment. If voriconazole is continued despite a phototoxic reaction, check the skin frequently and thoroughly to detect and manage pre-cancerous lesions as early as possible. Squamous cell carcinoma of the skin is usually associated with long term use. Stop voriconazole if pre-cancerous skin lesions or squamous cell carcinoma are identified. Note that patients may develop squamous cell carcinoma without a prior phototoxic reaction.
Visual adverse reactions (including blurred vison, photophobia, optic neuritis and papilloedema).	Usually reversible upon discontinuation of voriconazole.

The above list should not be considered exhaustive. For further documented ADRs and details of likelihood etc, see current Summary of Product Characteristics or BNF.

BASELINE INVESTIGATIONS:

- Liver function tests (specifically, aspartate transaminase [AST] and alanine transaminase [ALT] levels).
- Urea and electrolytes.
- Plasma calcium and magnesium.
- Electrocardiogram, if the patient has risk factors for QTc prolongation (refer to latest guidance)

MONITORING (PRIMARY CARE):

- The following monitoring is to be undertaken in Primary Care - this monitoring is required only after acute diarrhoeal illness.
- Routine monitoring will be undertaken by secondary care, as detailed separately.

Monitoring Parameters	Frequency	Laboratory results	Action to be taken
Urea and electrolytes including calcium and magnesium	Check electrolytes **following acute diarrhoeal illness.**	Hypokalaemia, hypomagnesemia and hypocalcaemia increase the risk of arrhythmias	Correct electrolyte disturbances promptly.

		(voriconazole has been associated with QTc interval prolongation).	

MONITORING (ACUTE SECTOR):

- Routine monitoring will be undertaken in Acute Care

Monitoring Parameters	Frequency	Laboratory results	Action to be taken
Liver function tests	At least weekly for the first month of treatment, monthly thereafter if there are no changes in the first month of treatment	Increases in AST and ALT indicate possible liver toxicity.	Discuss with responsible acute care prescriber. May require discontinuation of voriconazole if AST or ALT levels become markedly elevated.
Urea and electrolytes including calcium and magnesium	At the same time as LFTs. See above. Check electrolytes following acute diarrhoeal illness.	Hypokalaemia, hypomagnesemia and hypocalcaemia increase the risk of arrhythmias (voriconazole has been associated with QTc interval prolongation).	Correct electrolyte disturbances promptly.

PHARMACEUTICAL ASPECTS:

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COST:

PLEASE NOTE: All medicines included in a shared care protocol that meet the criteria for a "high cost expensive medicine" and are prescribed in accordance with the shared care protocol are automatically accounted for in the "high cost/ expensive medicines list" for budget-setting purposes. No additional action is therefore required by GPs to request funding. For those medicines which are the subject of a shared care protocol but which do not meet the high cost expensive medicines criteria, transfer of prescribing costs will be considered if this is appropriate.

The dose of voriconazole is variable between 100mg-300mg bd with a likely maximum treatment length of 6 months.

The most likely dose is 200mg bd, cost estimated for 6 months treatment at this dose is £13,233.36.

The maximum dose of 300mg bd would incur a cost of up to £19,849.68 for 6 months treatment.
The minimum dose of 100mg bd would incur a cost of £6,616.32 for six months treatment.

INFORMATION FOR COMMUNITY PHARMACIST:

Voriconazole is a licensed medicine which should be available from most wholesalers.

Voriconazole has many drug interactions, including over the counter and herbal medicines (some significant interactions are listed on page 3). Patients wishing to use over the counter medicines or herbal medicines known to interact with voriconazole should be referred to their GP.

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION:

Name	Designation	Acute Site	Department phone number
Dr Mark Cotton	Consultant Physician (Respiratory)	Glasgow Royal Infirmary	**0141 211 4803**
Dr Colin Clark	Consultant Dermatologist	Glasgow Royal Infirmary	0141 211 4297

SUPPORTING DOCUMENTATION:

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