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Title:	**Guidelines for the Administration of Methylthioninium Chloride for the Treatment of Ifosfamide Induced Encephalopathy in Adult Oncology and Haematology Patients**			
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Date	Version	Author	Comments
26/04/2018	0.1	L Edgar	Initial draft
	0.2	L. Edgar	Amended following comments from MPT
10/08/2018	0.3	L. Edgar	Amended following meeting with oncology and haematology medical teams
11/09/2018	0.4	L. Edgar	Amended following meeting with Ian Sturgess and review of literature
01/10/2018	1	L. Edgar	Final draft
15/02/19	1	L. Edgar	Approved at SACT CRG Meeting

1.0 INTRODUCTION / PURPOSE OF POLICY

1.1 Background

Ifosfamide is an alkylating agent used within SACT regimes for the treatment of sarcomas, lymphomas and germ cell tumours. Its use is limited due to potentially severe side effects, the most serious of which is Ifosfamide induced encephalopathy (IIE). Some degrees of central nervous system toxicity can occur in 10-30% of patients after administration of intravenous Ifosfamide.

Whilst the exact mechanism for IIE is unknown, it is thought that hepatic conversion of Ifosfamide to chloracetaldehyde is the main pathophysiological cause. Chloroacetaldehyde is capable of crossing the blood-brain barrier and is excreted by the kidneys.

1.2 Purpose

This policy outlines the protocol for the prescription and administration of Methylthioninium Chloride for the treatment of Ifosfamide induced encephalopathy in the adult oncology and haematology setting. The policy should be used in conjunction with the BHSCT Hospital Medicines Code. The Summary of Product Characteristics (SPC) or British National Formulary should be consulted prior to prescription and administration of Methylthioninium Chloride.

1.3 Objectives

The objective of this policy is to promote consistent clinical practice and raise awareness of potential cautions and toxicities in relation to the use of Methylthioninium Chloride in the treatment of Ifosfamide induced encephalopathy. .

2.0 SCOPE OF THE POLICY

This policy applies to all medical, nursing and pharmacy staff working within the adult oncology and haematology setting where Ifosfamide may be administered as part of a SACT regime.

3.0 ROLES/RESPONSIBILITIES

It is the responsibility of all staff involved in the prescribing, handling and administration of Ifosfamide and Methylthioninium Chloride to familiarise themselves with and adhere to this policy.

4.0 KEY POLICY PRINCIPLES

Definitions

Ifosfamide induced encephalopathy is a potential side effect of Ifosfamide, which is used in both the oncology and haematology setting.

Signs and symptoms of Ifosfamide induced encephalopathy

- Confusion, ranging from transient lethargy to delirium
- Hallucination or psychosis
- Incontinence and muscle twitching
- Less common manifestations include extrapyramidal symptoms, cranial nerve abnormalities, mutism, dysarthia, amnesia, blurred vision, hearing loss and aterixis.

Time to onset of IIE varies between 12-192 hours from the start of the Ifosfamide infusion. The following pre-treatment parameters are known to increase both the risk and severity of Ifosfamide induced encephalopathy.

- Low serum albumin
- High serum creatinine
- Presence of pelvic disease
- Previous cumulative dose of cisplatin
- Prior CNS disease
- Hypokalaemia
- Hyponatraemia.

Whilst the exact mechanism for IIE is unknown, it is thought that hepatic conversion of Ifosfamide to chloracetaldehyde is the main pathophysiological cause. Methylthioninium Chloride acts as an electron acceptor to prevent the formation of chloroacetaldehyde. Evidence suggests that Methylthioninium Chloride has a significant effect on recovery time from Ifosfamide induced encephalopathy.

Key Policy Statement(s)

Policy Principles

4.1 A licensed preparation of Methylthioninium Chloride (Proveblue) is available in the UK. It comes as 10ml ampoules containing methylthioninium chloride 5 mg/ml solution for injection. The use of Methylthioninium Chloride for the treatment of IIE is off-label.

4.2 Methylthioninium Chloride should be avoided where possible in patients who have been treated recently with serotonergic antidepressants including SSRIs, clomipramine and venlafaxine due to the risk of CNS toxicity. (This list is not exhaustive).

4.3 Within the oncology and haematology setting patients who are on SSRI's and other serotonergic drugs may require Ifosfamide as part of their SACT regime, for effective treatment of their cancer condition. There is a risk of these patients developing IIE which requires treatment with Methylthioninium Chloride.

4.4 Consideration should be given to discontinuing SSRI's and other serotonergic drugs for patients whose SACT regime includes Ifosfamide.

4.5 The prescriber should consider discontinuing drugs which may cause serotonin syndrome (BNF 74, appendix 1, Table 13) in patients who develop IIE and require treatment with Methylthioninium Chloride.

4.6 A consultant oncologist or haematologist should be contacted if central nervous system toxicity worsens whilst the patient is receiving Methylthioninium Chloride and dose reduction or discontinuation of Methylthioninium Chloride should be considered. This decision should only be made by a consultant.

4.7 Methylthioninium Chloride should be used with caution in patients with moderate to severe renal impairment.

4.8 Methylthioninium Chloride should be administered intravenously in 50ml 5% glucose over 15 minutes.

4.9 The severity of Ifosfamide induced encephalopathy is graded using the National Cancer Institute – Common Toxicity Criteria (NCI-TCC) grading for encephalopathy (see table 4.9.1)

Table 4.9.1

Grade	**1**	**2**	**3**	**4**
Symptoms	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life threatening consequences; urgent intervention required

4.10 Treatment of Ifosfamide induced encephalopathy with Methylthioninium Chloride depends on the severity of Ifosfamide induced encephalopathy.

4.11 The table below details treatment pathways for treatment of Ifosfamide induced encephalopathy.

Grade 1 encephalopathy • Monitor neurological status every 30 minutes • Ensure Ifosfamide infusion is running no faster than 1g/m2/hour
Grade 2 encephalopathy • Monitor neurological status every 30 minutes • Ensure Ifosfamide infusion is running no faster than 1g/m2/hour • Continue Mesna Infusion at prescribed rate • Commence intravenous Methylthioninium Chloride 50mg 4 hourly

• Monitor BP regularly and daily ECG whilst receiving Methylthioninium Chloride. • Continue Methylthioninium Chloride until encephalopathy has completely resolved • Consider prophylactic Methylthioninium Chloride for subsequent cycles of Ifosfamide • If signs and symptoms of IIE worsen contact consultant and consider potential side effects of Methylthioninium Chloride. Consider discontinuing Methylthioninium Chloride.
Grade 3-4 encephalopathy • Stop Ifosfamide Infusion. • Continue Mesna as prescribed • Monitor neurological status every 30 minutes • Commence Intravenous Methylthioninium Chloride 50mg 4 hourly • Monitor BP regularly and perform daily ECG whilst receiving Methylthioninium Chloride. • Continue Methylthioninium Chloride until encephalopathy has completely resolved • Consider other supportive measures/ICU review • Further treatment with Ifosfamide should be avoided. • If signs and symptoms of IIE worsen contact consultant and consider potential side effects of Methylthioninium Chloride. Consider discontinuing Methylthioninium Chloride.

4.12 If the use of methylthioninium chloride cannot be avoided in patients treated with serotenergic medicinal products the lowest possible dose should be chosen and the patient monitored closely for central CNS effects for up to 4 hours after administration.

4.12 The prophylactic treatment of IIE with Methylthioninium Chloride should be considered for patients who
- Have had previous grade 1 or grade 2 IIE
- Patients with a serum creatinine >150umol/L or serum albumin <30

4.13 For prophylactic treatment administer 50mg Methylthioninium Chloride intravenously 6 hourly for duration of Ifosfamide infusion.

5.0 IMPLEMENTATION OF POLICY

5.1 Dissemination

This policy has been agreed by the relevant medical teams and the SACT Multi-professional team (MPT) and disseminated at haematology and oncology safety meetings. It will be available on the BHSCT intranet for use by all medical, pharmacy and nursing staff.

5.2 Resources

Training and awareness of this policy will take place through the SACT MPT, relevant ward sisters and haematology and oncology Safety meetings.

5.3 Exceptions

There are no exceptions to this policy.

6.0 MONITORING

Any deviation from this policy will be recorded on the BHSCT incident reporting system via DATIX and tabled at Departmental Governance and Safety meetings.

7.0 EVIDENCE BASE / REFERENCES

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8.0 CONSULTATION PROCESS

Consultation for this policy was through the SACT multi professional group, which includes medical, pharmacy, nursing and senior management representation. In addition, relevant oncology and haematology medical teams were consulted.

9.0 EQUALITY STATEMENT

In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out. The outcome of the Equality screening for this policy is:

Major impact ☐

Minor impact ☐

No impact. ☒

SIGNATORIES
(Policy – Guidance should be signed off by the author of the policy and the identified responsible director).

L Edgar

_____ **Date:** 02/10/2018

Author

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_____ **Date:** 02/10/2018

Director