Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

[For all products in Annex I, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]

Summary of product characteristics

[…]

4.4 Special warnings and precautions for use

[A warning should be revised as follows]

Encephalopathy and CNS toxicity

Administration of ifosfamide can cause encephalopathy and other neurotoxic effects.

An ifosfamide-induced CNS toxicity may become manifest within a few hours to a few days after administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. If CNS toxicity develops, administration of ifosfamide should be discontinued.

The symptoms may include the following: confusion, somnolence, coma, hallucination, blurred vision, psychotic behaviour, extrapyramidal symptoms, urinary incontinence and seizures.

CNS toxicity seems to be dose dependent. Risk factors for the development of ifosfamide-associated encephalopathy include hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease and previous or concomitant nephrotoxic treatments including cisplatin.

Due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics or antihistamines) must be used with particular caution or, if necessary, be discontinued in case of ifosfamide-induced encephalopathy.

Patients treated with <Product Name> should be closely monitored for symptoms of encephalopathies in particular if patients are at increased risk for encephalopathies.

The use of methylene blue may be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies.

[Conflicting information on the risk of encephalopathy and CNS toxicity included in other sections should be removed.]

[For other sections, the MAHs are also reminded of the obligation to maintain their product information up to date in accordance with Article 23 of Directive 2001/83/EC, including in line with information included in the PI of the reference medicinal product.]

[…]

Package leaflet

[…]

2. What you need to know before you are given <Product Name>

[The below warnings should be displayed in this section. It is noted that information regarding impaired renal function is already reflected.]

Warnings and precautions

Talk to your doctor before you are given <Product Name>:

[…]

- if you have or had treatment with cisplatin before or during ifosfamide treatment

[…]

Ifosfamide can have toxic effect on the brain and spinal cord and cause encephalopathy (non-inflammatory brain disease). Tell your doctor immediately if you experience any of the following, which may be signs of brain and spinal cord toxicity:

- confusion, sleepiness, unconsciousness/coma, hallucination/delusion, blurred vision, perception disorders, extrapyramidal symptoms (like continuous spasms, muscle contractions, motor restlessness, slowness of movement, irregular movements), lack of control over passing urine and seizures.

Your doctor or nurse may monitor you for signs and symptoms of brain and spinal cord toxicity.

[…]

Other medicines and <Product Name>

Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell them if you have taken the following medicines:

[…]

- medicines with an effect on the brain such as those against vomiting and nausea, sleeping pills, certain painkillers (opioids), or allergy medicines