衛署藥輸字第 018481、018480、018479 號

“愛斯達”好克癌® 注射劑

500 公絲、1 公克、2 公克

Holoxan® 500mg、1g、2g

成　　份：

每小瓶含 ifosfamide 500mg、1g、2g 乾粉，可配製成注射溶液。

適 應 症：

支氣管癌、睪丸癌、軟組織肉瘤 (平滑肌肉瘤、橫紋肌肉瘤、軟骨肉瘤)、骨肉瘤、乳癌、子宮內膜癌、腎上腺癌及惡性淋巴癌之緩解。

禁 忌 症：

- 已知對 ifosfamide 過敏者
- 骨髓功能被嚴重的抑制(特別是患者曾接受 cytotoxic agent 或放射線治療者)
- 感染性疾病患者
- 腎功能受損或尿道阻塞
- 膀胱炎
- 懷孕
- 授乳

警　　告：

開始治療前，需先排除尿道阻塞、膀胱炎、各種感染症和校正不平衡之電解質。一般而言，Holoxan 如同其他 cytostatics，應謹慎用於虛弱或老年人和曾接受放射線治療的患者。免疫系統較弱之患者，如糖尿病、慢性肝腎功能受損者，也需要特別的照顧。如病人出現腦轉移、腦部症狀和(或)腎功能惡化之現象，則必須接受持續密切的觀察。

懷孕及授乳期之使用

基於生存的前題，懷孕第一期是否要進行流產之醫療上考量是絕對需要的。懷孕第一期後，如治療不能延後，且病人又希望持續懷孕，在告知病人有導致畸胎的可能性之後，才可進行化學治療。Holoxan 治療期間不得授乳。

避孕措施

Ifosfamide 可能會引起先天之異常。治療期間並不建議受孕。男性在接受 Holoxan 治療之前，可以先貯存精子。女性不應在治療期間懷孕。如果在治療期間懷孕，應尋求遺傳學上之諮詢。化學治療結束後的避孕期，要依初次發病的預後和患者想要小孩的程度而定，但遺傳之諮詢應被列入考慮。

副 作 用：

使用 Holoxan 治療之患者可能會有下列之副作用：

骨髓抑制

依劑量而發生不同程度之骨髓抑制作用(白血球、血小板減少症和貧血)。白血球減少會引起危及生命之感染的危險，而血小板減少症會引起出血之危險，因此要謹慎考慮用藥安全。一般在治療後一至二星期，白血球與血小板數目會降至最低，而在三至四星期間會復原。貧血經常發生在數次的治療週期後。併用其他骨髓抑制劑可能需要調整劑量。單一高劑量治療引起白血球減少之頻率會高於依比例調整劑量之治療。接受化學和(或)放射線治療及腎功能不良的患者，發生嚴重之骨髓抑制的機會更為顯著。ifosfamide 如同其他的 cytostatics，在每次化學治療週期前和週期間均需考慮血球數目，依血球圖(blood picture)而採適合的劑量調整。

發生骨髓抑制時，其劑量調整如下：

白血球數目	血小板數目	
> 4000	> 100,000	計劃劑量之 100%
4000 - 2500	100,000 - 50,000	計劃劑量之 50%
< 2500	< 50,000	停止給藥直到正常為止或依醫師決定

尿毒性和腎毒性

使用 ifosfamide 常發生與劑量有關之出血性膀胱炎(輕度到重度)。

說明

劑量之調整、攝取充足的水份、保持體液平衡，特別是併用 mesna 治療，能夠顯著的降低出血性膀胱炎的嚴重性及發生頻率。

腎小球功能障礙，隨血清肌酸酐之增加而發生，肌酸酐清除率降低與蛋白尿會經常發生，血胺酸過多之腎小管功能障礙、磷酸鹽尿、酸中毒或蛋白尿發生頻率更高。嚴重的腎病較為罕見。發生腎小球功能異常之危險因素，可能是服用高劑量的藥物和額外的接受含鉑藥物的治療。腎小管功能異常之原因可能是腎切除、額外的接受含鉑的藥物或併用放射線治療腹部的腎或經切除後餘留的腎。要謹慎併服具潛在腎毒性之藥物如 aminoglycosides, acyclovir 或 amphotericin B。這些藥物對腎小管不具潛在之毒性，但可能導致腎小球功能之惡化。有一些較罕見的例子，具慢性腎小管疾病之患者可能會出現 Fanconi's syndrome，而造成佝僂病或成人之軟骨病。其造成原因是藥物的高劑量累積結果及孩童年紀太小(特別是三歲以下)。故開始治療前、間及治療後，必須評估與確定腎小管與腎小球之功能。在長期的 ifosfamide 治療期間，給予足夠的利尿劑和規律的控制腎功能是有必要的，此特別指孩童。如果開始治療時即有腎病，再連續以 ifosfamide 治療可能會發生不可逆的腎疾病。因此謹慎的評估使用本藥的利弊是必須的。

要特別注意腎切除、腎功能不全和服用具腎毒性(eg. cisplatin)藥物之患者，因這些病人接受治療會使骨髓毒性、腎毒性及腦部毒性之強度與發生頻率增加。

中樞神經系統

有 10-20% 的病例，開始治療後之數小時至數日後發生腦病變。危險因子包括健康情況不佳，腎功能受損(creatinine > 1.5mg/dl)，治療前使用具腎毒性之藥品(eg. cisplatin)，以及治療後腎阻塞(如骨盆腫瘤)。其他可能的危險因子有：年紀太大、具酗酒歷史、血清蛋白或碳酸氫根濃度減少，肝功能障礙或併用高劑量的止吐藥物治療。腦病變最常見的是：困倦，可能發展成幻覺或昏迷狀態。其他症狀有虛弱、健忘、精神抑鬱、定向力障礙、焦躁不安、精神混亂、幻覺、小腦症狀、失禁和痙攣。腦病變通常是可逆的，且於停止 ifosfamide 投予後數日內即會消失。嚴重的症狀是極罕見的，只有在極少數案例中有死亡報告且是因投予相當高的劑量。依比例而調整劑量，將可使腦疾患發生之頻率與嚴重性降低。

說明

因 ifosfamide 具中樞神經毒性，因此病人必須被小心監測。要是發生腦病變，則 ifosfamide 治療必須停止。假如腦病變是由 ifosfamide 所引起的，則作用於中樞神經系統的藥物(如止吐劑、鎮靜劑、麻醉藥或抗組織胺)亦應停止，或要特別小心使用。

其他的不良反應

噁心、嘔吐是與劑量有關之副作用，約有 50%病例會出現中等到嚴重的症狀。掉髮是另一種發生頻率較高且可逆的副作用，發生率可達 100%，其與劑量及治療持續時間有關。由於其烷化作用機轉，Holoxan 會引起部份不可逆之因精子活動力不足，或持續的精液過少而導致精子生成受損。而因停經和女性荷爾蒙濃度減少，所引起的不可逆排卵障礙之發生頻率較低。

除此之外，還可能發生以下之不良反應：

- 有慢性肺部組織纖維病變之病例。肺水腫發生過一例。
- 曾發生過伴隨血鈉過少或尿滯留之 SIADH(抗利尿激素分泌不足之症狀，Schwartz-Bartter Syndrome)。低血鉀症僅發生過一例。
- 有急性胰臟炎之病例。
- 罕見病例有：皮膚和黏膜發炎反應。
- 罕見病例有過敏反應，及更進一步發生休克。
- 罕見案例有視覺模糊和暈眩。

有時候亦會發生肝酵素或膽紅素濃度增加，而厭食、腹瀉、便秘、靜脈炎或發熱可能較少見。多種神經疾病、肺炎、視覺不良或對幅射反應增強亦不常見。投予高劑量之ifosfamide後或於治療前、治療時併用anthracyclines，亦有心室節律不整、ST-T segment改變或心衰竭現象。由以上觀點視之，要再次強調規律的監測電解質之需要，且要特別注意有心臟病史之患者。如一般的cytotoxic治療，特別是烷化基劑，使用ifosfamide治療亦有復發腫瘤的危險性。

注意事項：

下列方法和(或)試驗可用於抑制或減輕副作用：

- 適時的服用止吐劑。
- 規律的測量血球數目。
- 規律的檢測腎功能之參數。
- 規律的檢測尿液分析值和尿液沉澱。
- 治療開始前如有肝或腎功能不全，Holoxan之使用應依患者作個別的考量。建議使用Holoxan治療的患者應隨時監測其肝腎功能。
- 為修正糖尿病患者之降血糖藥的劑量，應規律的檢測其血糖濃度。
- 使尿液適當的增加是有必要的。
- 如有發熱和(或)白血球減少現象，則需投予抗生素或抗黴菌藥物。
- 治療期間需特別注意口腔保健。

駕車或操作機械

服用Holoxan可能會影響患者駕車或操作機械的能力。這可能直接肇因於藥物所引起之腦病變，或間接肇因於噁心、嘔吐，特別是併服作用於中樞神經系統之藥物或酒精。

交互作用：

與其他cytostatics或放射線治療而產生之交互作用，會使骨髓毒性增加。ifosfamide亦可能因幅射之作用而使皮膚反應增強。

先前使用或併用具腎毒性之藥劑如cisplatin、aminoglycosides、acyclovir或amphotericin B可能會使ifosfamide之腎毒性、血中毒性及神經毒性增加。由於ifosfamide之免疫抑制作用，會使預防接種產生不良反應，其傷害可由活病毒接種所引起。ifosfamide會使warfarin之抗凝血作用增加，並導致出血之危險。

與cyclophosphamide類似，可能會產生以下的交互作用：

- 如併用allopurinol或hydrochlorothiazide可能會增強骨髓抑制作用。
- 併用chlorpromazin、triiodothyronine或aldehyde dehydrogenase抑制劑(如disulfiram)，會增強其作用與毒性。
- 會增加sulfonylureas之降血糖作用。
- 先前使用或併用phenobarbital、phenytoin或chloral hydrate，會誘發肝微粒體酵素的作用，而使ifosfamide代謝加速。
- 亦可能會增加suxamethonium之肌肉鬆弛作用。

用法與用量：

本藥限由醫師使用

本藥限由具治療經驗之腫瘤專科醫師使用。

劑量依患者而做個別之調整。單一藥物治療下，最常見之治療方式是依比例而調整。在缺乏個別使用經驗下，建議可採用以下之方法：

一般Holoxan以靜脈注射投予，每天以1.2-2.4 g/m^{2}體表面積(至60 mg/kg體重)分成數次投予，連續投予五天(依注射量而定，注射時間約30-120分鐘)。Holoxan也可能投予單一高劑量，24小時連續輸注。而每週期一般劑量為5g/m^{2}體表面積(125 mg/Kg體重)，且不應超過8 g/m^{2}體表面積(200 mg/Kg體重)。須注意單一高劑量可能引起較高的血液毒性、尿毒性、腎毒性和中樞神經系統毒性。務必要注意溶液中ifosfamide濃度不能超過4%。若併用其他cytostatics治療，劑量應依治療表依不同型態而作調整。

說明

由於本藥具尿道毒性，原則上 ifosfamide 應合併 mesna 使用。而其他因 ifosfamide 產生之毒性或療效，均不會受 mesna 所影響。治療期間若發生伴隨輕微或嚴重的血尿之膀胱炎，應立即停止用藥，直到病人復原為止。由於 ifosfamide 之細胞抑制，僅發生在肝臟中之活化作用後，所以若採靜脈旁注射不會有傷害組織之危險。

服藥與治療期間

治療週期可每 3-4 星期重覆一次。間隔將依血球數、不良反應與副作用之復原情形而定。並應持續依指示給予尿道保護劑 mesna。規律的測量血球數目、腎功能、尿液分析(包括尿沉澱)是必須的。依指示適時的服用止吐劑是必要的。要密切注意 Holoxan 與止吐劑併用對中樞神經系統所產生之影響。

注射液之配製：

處理 Holoxan 時須與處理其他 cytotoxic 製劑的安全須知相同。

將注射用水依下列的量加入乾粉中，以配製 4%注射用之等張溶液：

Holoxan	500mg	1g	2g
Water for injection	13ml	25ml	50ml

注射用水加入後強力振搖 0.5-1 分鐘即可溶解。如果沒有立刻完全溶解，將溶液靜置幾分鐘以待其溶解。配製好的溶液如放在溫度不超過 8°C 的冰箱內，則可保存 24 小時。Holoxan 短期靜脈輸注液(約 30-120 分鐘)之配製，是以 250ml 之 Ringer's solution 或 5% glucose solution 或生理食鹽水稀釋。而超過 1-2 小時之長時間輸注液，建議以 500ml 之 Ringer's solution 或 5% glucose solution 或生理食鹽水稀釋。持續 24 小時之高劑量 Holoxan 輸注液之配製，如 5g/m^2，必須以 5% gulcose solution 和(或)生理食鹽水稀釋成 3 公升溶液。

說明：

因 ifosfamide 具烷化作用，故其有致突變性，也具潛在的致癌性。配製時應避免接觸到皮膚和黏膜。

貯存之注意事項：

- Holoxan 之貯存不可超過 25°C。
- 如超過包裝上所示之有效期限，請勿再使用。
- 配製好的溶液請於 24 小時內使用(貯存勿超過 8°C)。
- 請將藥品遠離孩童存放。

包　　裝：

500mg、1g、2g 小瓶裝，100 小瓶以下盒裝。

製造廠：Baxter Oncology GmbH
廠　址：Kantstrasse 2, D-33790 Halle - künsebeck , Germany
藥　商：百特醫療產品股份有限公司
地　址：台北市敦化南路二段 216 號 15 樓
電　話：(02) 2378-5000

– in rare cases inflammation of the skin and mucous membrane
– in rare cases hypersensitivity reactions, in isolated cases with fever and progressing to shock
– in rare cases blurred vision and episodes of dizziness

An increase in liver enzymes and/or in the bilirubin level can also occur occasionally. Anorexia, diarrhea, constipation, phlebitis or pyrexia may more seldom be seen. Polyneuropathy, pneumonitis, impaired vision or an increased reaction to radiation were isolated seen. There have been isolated reports of supraventricular or ventricular arrhythmias, ST-T segment changes and heart failure after very high doses of ifosfamide and/or after pretreatment or concomitant treatment with anthracyclines. In this context, it is again necessary to stress the need for regular electrolyte monitoring and special caution when treating patients with history of heart disease. As with cytotoxic therapy in general, especially with alkylating agents, treatment with ifosfamide involves the risk of secondary tumours as late sequelae.

Precautions:
The following measures and/or tests are indicated in order to limit or alleviate adverse reactions:
– Timely administration of antiemetics,
– Regular blood counts,
– Regular checks of renal function parameters,
– Regular check of urinalysis and urinary sediment.

In cases of hepatic or renal impairment before the start of therapy, the use of Holoxan has to be individually weighed for each patient. It is recommended that patients under Holoxan-therapy are monitored more frequently.
The blood sugar level should be checked regularly in diabetics in order to modify the antidiabetic therapy on time.
It is essential to ensure adequate diuresis.
Fever and/or severe leucopenia require prophylactic administration of antibiotics and/or antimycotics.
Attention should be paid to meticulous oral hygiene.

Effects on ability to drive and use machines:
Holoxan may affect a subject's ability to drive a motor vehicle or to operate machinery. This may occur either directly by induced encephalopathy or indirectly as a result of nausea and vomiting, especially when CNS-active drugs or alcohol are taken concomitantly.

Interactions with other drugs:
Myelotoxicity can be increased as a result of interaction with other cytostatics or radiation. Ifosfamide may intensify skin reactions due to irradiation.
The prior or concurrent administration of nephrotoxic agents like cisplatin, aminoglycosides, acyclovir or amphotericin B may enhance the nephrotoxic effect of ifosfamide and consequently haematotoxic and neurotoxic (CNS) effects as well.
Because of the immunosuppressive effect of ifosfamide, an impaired response to the respective vaccine may occur. Vaccination injury can be caused by live-virus vaccinations.
The concurrent use of ifosfamide may increase the anticoagulant effect of warfarin and thus raise the risk of haemorrhages.
In analogy with cyclophosphamide, the following interactions seem possible:
– The myelosuppressive action may be enhanced by the concurrent administration of allopurinol or hydrochlorothiazide.
– The effect and the toxicity may be enhanced by the concurrent administration of chlorpromazin, triiodothyronine or aldehyde dehydrogenase inhibitors such as disulfiram.
– The treatment may increase the hypoglycaemic actions of sulfonylureas.
– Prior or concurrent treatment with phenobarbital, phenytoin or chloral hydrate involves the possibility of microsomal liver enzyme induction and thus a faster metabolism of ifosfamide.
– The treatment may increase the muscle-relaxant effect of suxamethonium.

Dosage and administration:
The treatment should only be administered by an experienced oncologist. The dosage must be adapted to each patient individually. In single-drug therapy of adults, the most common treatment is based on fractionated doses. In the absence of individual prescriptions, the following recommendations may serve as a guideline.
In general, Holoxan is given intravenously in divided doses of 1.2–2.4 g/m² body surface (up to 60 mg/kg of body weight) daily for 5 consecutive days (the duration of these infusions is about 30–120 minutes, depending on the volume). Holoxan may also be given in a single high dose, usually as a 24-hours-prolonged infusion. The dosage is generally 5 g/m² body surface (125 mg/kg body weight) and should not exceed more than 8 g/m² body surface (200 mg/kg body weight) per cycle.
A single high dose may cause higher haemato-, uro-, nephro- and CNS toxicity.
Care should be taken to ensure that the ifosfamide concentration of the solution does not exceed 4 percent.
In combination-therapy with other cytostatics, the dose should be adapted to the type of therapeutic scheme.

Remarks:
Because of its urotoxicity, ifosfamide should as a matter of principle be used in combination with mesna. Other toxicities and the therapeutic effects of ifosfamide will not be influenced by mesna.
Should cystitis with micro- and macrohaematuria develop during therapy, the treatment should be discontinued until the patient has recovered.
Because the cytostatic effect of ifosfamide occurs only after activation in the liver, there is no danger of injuring the tissue in the case of paravenous injections.

Administration and duration of treatment:
The therapy cycles may be repeated every 3–4 weeks. The intervals will depend on the blood count and on the recovery from any adverse reactions or side-effects.
The administration of uroprotection with mesna (Uroprotector®, Uromitexan®) as directed, should be maintained.
Regular blood counts, regular checks of renal function and regular urinalysis including urinary sediment are necessary.
Timely administration of antiemetics is indicated, and the additional influences on the CNS in combination with Holoxan should be taken into consideration.

Preparation of the solution:
The handling of Holoxan should always be in accordance with the safety precautions used for the handling of cytotoxic agents.
To prepare a 4% isotonic solution ready for injection, water for injection is added to the dry substance in the following amounts:

Holoxan	200 mg	500 mg	1 g	2 g
Water for injection	5 ml	13 ml	25 ml	50 ml

The substance dissolves readily if the vials are vigorously shaken for 0.5 to 1 min after addition of the water for injection. If the substance fails to dissolve immediately and completely, it is advisable to allow the solution to stand for a few minutes. The prepared solution can be kept for up to approx. 24 hours if stored at a temperature not exceeding +8 °C (refrigerator). The Holoxan solution for short-term intravenous infusion (approx. 30–120 min) is prepared by diluting the above solution with 250 ml Ringer's solution or 5% glucose solution or physiological saline. For longer infusions over one to two hours, dilution is recommended with 500 ml Ringer's solution or 5% glucose solution or physiological saline. For continuous 24-hour infusions of high-dose Holoxan, the prepared Holoxan solution, e.g., 5 g/m², must be diluted to 3 litres with 5% glucose solution and/or physiological saline.

Special remark:
Because of its alkylating action, ifosfamide is a mutagenic and also a potential carcinogenic substance. Contact with the skin and mucous membranes should therefore be avoided.

Stability note:
Holoxan should not be stored above +25 °C!
Holoxan should not be used after the expiry date stated on the package.
The reconstituted solution should be used within 24 hours after preparation (do not store above + 8°C!).

Store drugs out of children's reach !

Name and permanent address of the manufacturer and the holder of the marketing authorization
Baxter Oncology GmbH
Daimlerstraße 40
60314 Frankfurt, Germany
Phone: +49 69-9686 60 00

Date of last revision of the text
January 2002

Presentation:
200 mg vials – Packs of 10 vials
500 mg vials – Packs of 1 and 10 vials
1g vials – Packs of 1 and 10 vials
2g vials – Packs of 1 and 10 vials

Holoxan® is available on prescription only

Baxter

Patient Information Leaflet
Please read carefully!

Baxter Oncology GmbH
Frankfurt am Main
Germany Allemagne Alemania

Holoxan®

Active substance: Ifosfamide

Composition:	1 vial	Holoxan 200 mg	Holoxan 500 mg	Holoxan 1 g	Holoxan 2 g
		contains:			
	Ifosfamide	200 mg	500 mg	1 g	2 g

as dry substance for preparing an injectable solution.

Indications:
Holoxan is to be administered exclusively by physicians with experience in oncology. It is indicated in inoperable malignant tumours that are sensitive to ifosfamide, e.g. bronchial carcinoma, ovarian carcinoma, testicular tumours, soft-tissue sarcoma, breast cancer, pancreatic carcinoma, hypernephroma, endometrial carcinoma, malignant lymphomas.

Special remark:
Should during treatment with Holoxan a cystitis in connection with macro- or microhaematuria appear, Holoxan therapy has to be interrupted until normalization.

Contraindications:
Holoxan is contraindicated in cases of
– known hypersensitivity to Ifosfamide
– severely depressed bone-marrow function (especially in patients previously treated with cytotoxic agents or radiotherapy)
– active infections
– impaired renal function and/or obstructions of the urine flow
– cystitis
– pregnancy (see special comments)
– lactation

Remarks:
Before starting treatment, it is necessary to exclude or correct any obstruction of the efferent urinary tract, cystitis, infections and electrolyte imbalances. In general, Holoxan®, like other cytostatics, should be used with care in weakened or elderly patients and in patients who have had previous radiotherapy. Patients with a weakened immune system, e.g. those with diabetes mellitus, chronic hepatic and renal impairments, also require special care. Patients with brain metastases, cerebral symptoms and /or deteriorated renal function must be kept under close observation.

Use during pregnancy and lactation
In a vital indication during the first trimester of pregnancy a medical consultation regarding abortion is absolutely necessary.
After the 1st trimester of pregnancy, if therapy cannot be delayed and the patient wishes to continue with her pregnancy, chemotherapy may be undertaken after informing the patient of the minor but possible risk of teratogenic effects.
Mothers must not breast feed during treatment with Holoxan.

Contraceptive measures
Ifosfamide can cause congenital anomalies. Conception during treatment is not advisable. Men to be treated with Holoxan should be informed about sperm preservation before treatment. Women should not become pregnant during treatment. Should they still conceive during treatment, they should seek genetic consultation. The duration of contraception after the end of chemotherapy depends on the prognosis of the primary disease and on the intensity of the parents' desire for a child. The possibility of a genetic consultation should be used.

Side-effects:
Patients on Holoxan therapy may experience the following side-effects:

Myelosuppression:
Different degrees of myelosuppression (leucocytopenia, thrombocytopenia and anaemia) can occur, depending on the dose. Frequently leucocytopenia with the risk of life-threatening infections and thrombocytopenia with the risk of bleeding have to be taken into consideration. The lowest leucocyte and thrombocyte counts normally occur one to two weeks after start of treatment and recover within 3 to 4 weeks. Anaemia usually occurs after several cycles of treatment. A combination treatment with other myelosuppressive agents may require dose adjustments. Single high-dose treatment leads more frequently to leucocytopenia than fractionated dose-regimen. In pretreated (chemotherapy and/or radiotherapy) patients or patients with renal function impairment, a more severe myelosuppression can be expected. With ifosfamide as with other cytostatics, blood counts have to be taken before each chemotherapy cycle as well as during the intervals between cycles. Depending on the blood picture, appropriate dose adaptations (see table) should be made.

Remark: Guidelines for dose reduction in myelosuppression

Leucocyte Count	Thrombocyte Count	
> 4000	> 100 000	100% of planned dose
4000 – 2500	100 000 – 50 000	50% of planned dose
< 2500	< 50 000	postponement until normalisation or individual decision

Urotoxicity and nephrotoxicity:
Haemorrhagic cystitis (macro- and microhaematuria) is a frequent, dose-dependent complication of Ifosfamide.

Remark:
Fractionated dosing, adequate hydration, maintenance of fluid balance and particularly concomitant treatment with mesna (Uromitexan®) can markedly reduce the frequency and severity of haemorrhagic cystitis.
Disorders of glomerular renal function with an increase in serum creatinine, a decrease in creatinine-clearance and proteinuria can occasionally occur, or more frequently disorders of tubular renal function with hyperaminoacidiuria, phosphaturia, acidosis or proteinuria. Severe nephropathies are rare. Possible risk factors for disorders of glomerular renal function are high doses of the drug and additional treatment with platinum containing drugs. Risk factors for disorders of tubular renal function are previous nephrectomy, additional treatment with platinum containing drugs or concomitant irradiation of the abdomen with inclusion of the kidneys or the remaining kidney. Caution is advisable when potentially nephrotoxic drugs such as aminoglycosides, acyclovir or amphotericin B are used concomitantly. These drugs do not potentiate the tubular kidney disorder, but may cause further deterioration of glomerular function.
In rare cases, patients with chronic tubular kidney disorder may develop Fanconi's syndrome resulting in rickets or, in adults, osteomalacia. Predisposing factors are high cumulative doses of the drug and young age (particularly younger than 3 years). Glomerular and tubular kidney function must therefore be evaluated and checked before start of therapy, during and after therapy.
During long-term treatment with ifosfamide, sufficient diuresis and regular control of renal function is necessary. This applies especially to children. In case of beginning nephropathy, irreversible kidney damage has to be expected if treatment with ifosfamide is continued. A careful risk-benefit evaluation is required.
Caution is required in unilaterally nephrectomized patients, in patients with impaired renal function and in patients pretreated with nephrotoxic drugs (e.g. cisplatin). In these patients frequency and intensity of myelotoxicity, nephro- and cerebral toxicity are increased.

Central nervous system:
In 10–20% of cases, encephalopathy occurs and develops within a few hours up to a few days after start of treatment. Risk-factors are a poor state of health, impaired renal function (creatinine > 1.5 mg/dl), pre-treatment with nephrotoxic drugs (e.g. cisplatin) and post-renal obstructions (e.g. pelvic tumors). Other possible risk-factors are old age, a history of alcohol abuse, decreased levels of serum albumin or hydrogen carbonate, hepatic dysfunction or concurrent high dose treatment with antiemetic drugs. The most common symptom of encephalopathy is drowsiness which can progress to somnolence and coma. Other symptoms can be weakness, forgetfulness, depressive psychoses, disorientation, restlessness, confusion, hallucinations, cerebellar symptoms, incontinence and convulsions. The encephalopathies are usually reversible and disappear spontaneously within a few days after the last ifosfamide administration. Severe courses are rare, and deaths were only seen in isolated cases and in connection with very high doses of the drug. With a fractionated dose-regimen, encephalopathies are less frequent and less severe.

Remarks:
Due to the CNS-toxicity of ifosfamide, patients must be carefully monitored. In the event of encephalopathy, ifosfamide treatment has to be discontinued and must not be resumed. In case of ifosfamide induced encephalopathy, drugs acting on the CNS (e.g., antiemetics, tranquilizers, narcotics or antihistamines) should be discontinued if possible, or used with special caution.

Other adverse effects:
Nausea and vomiting are dose-dependent side-effects. Moderate to severe forms can be seen in about 50% of the cases. Another frequent side-effect is reversible alopecia which occurs in up to 100% of patients, depending on dosage and duration of treatment. Because of its alkylating mechanism of action, Holoxan can cause partly irreversible impairment of spermatogenesis with resulting azoospermia or persistent oligospermia, respectively less frequently irreversible ovulation disturbances with resulting amenorrhea and reduced levels of female sex hormones.

Additionally, there can occur:
– in isolated cases chronic interstitial pulmonary fibrosis. Toxic-allergic pulmonary oedema was reported in one single case.
– in isolated cases SIADH (syndrome of inadequate ADH-secretion, Schwartz-Bartter-syndrome) with hyponatremia and water retention. Hypokalemia was reported in one single case.
– in isolated cases acute pancreatitis

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