IS1300TW01

易立顯350注射液

(350毫克碘/毫升)

Xenetix 350 Injectable solution (350mg I/ml)

【衛署藥輸字第023931號】

本藥限由醫師使用

1.產品名稱

易立顯350 注射液

2.定性定量組成

每100毫升溶液

Iobitridol ..... 76.78克 (767.8 毫克/毫升)

相當於含碘 ..... 35克 (350 毫克/毫升)

- 每毫升碘含量 : 350毫克
- 於20℃粘度 : 21厘泊
- 於37℃粘度: 10厘泊
- 滲透壓 : 915 mOsm/kg H_2O
- 每50毫升小瓶裝碘含量 : 17.5克
- 每100毫升小瓶裝碘含量 : 35克
- 每200毫升瓶裝碘含量 : 70克
- 每500毫升瓶裝碘含量 : 175克

賦形劑已知具作用者 : Sodium (每100毫升可達3.5 毫克). 完整表列, 見6.1節

3.劑型

注射用溶液

4.臨床特性

4.1.適應症

本產品僅用於診斷

用於成人及兒童之

- 靜脈內尿路攝影 ;
- 腦部及全身電腦斷層掃描 ;
- 靜脈內數位消減血管攝影 ;
- 動脈攝影 ;
- 心血管攝影檢查 。

4.2 用法用量及給藥方法

使用劑量須配合檢驗方式，檢驗部位與受檢驗者的體重與腎功能，尤 其是使用於兒童的檢驗時須特別注意。

建議劑量如下 :

適應症	平均劑量 (毫升/公斤)	總量(最小值/最大值)毫升
尿路攝影	1.0	50–100
電腦斷層掃描 腦部 全身	 1.0 1.8	 40–100 90–180
靜脈內數位消減血管攝影	2.1	95–250
動脈攝影 周邊 下肢 腹部	 2.2 1.8 3.6	 105–205 80–190 155–330
心血管攝影檢查 成人 兒童	 1.9 4.6	 65–270 10–130

4.3. 禁忌

- 已知對iobitridol 或"6.1賦形劑清單" 所列任何賦形劑過敏
- 曾對本品Xenetix 350注射液有嚴重立即或延遲性皮膚過敏反應 (見4.8不良反應).
- 有甲狀腺毒症(thyrotoxicosis)表現者.

4.4. 特殊警語及使用注意事項

- 不論以何種途徑給藥或劑量, 皆存在過敏風險.
- 局部給藥使體腔不透明而產生過敏的風險並不清楚:

a) 由特定途徑給藥 (關節, 膽, 腦脊髓膜內, 子宮內等.) 而形成不同程度全身性擴散,即可能觀察到全身性作用.

b) 經口或直腸給藥, 正常情形下產生非常有限的全身性擴散. 如果腸道黏膜正常, 不超過5%給藥劑量會出現在尿液中, 其餘則由糞便排除. 相反地, 如果腸道黏膜受損, 吸收會增加. 如果是穿孔, 則吸收快速且全面並擴散至腹膜腔, 並且從尿液排除. 此劑量相關的全身性作用與腸道黏膜的狀態有關.

c) 然而, 過敏免疫機轉則與劑量無關, 可能發生於任何時間, 而且與給藥途徑無關.

無特殊研究需要時，本品Xenetix不可用於脊髓攝影. 所有含碘造影劑可能會導致輕微、嚴重或有致死可能之反應，有時會 立即發生(60分鐘內)，有時會延遲出現 (7日內)；這些反應通常無法預 期，但較常發生在有過敏病史 (尊麻疹、氣喘、乾草熱、濕疹，各種不同之食物或藥物過敏)，或曾 接受含碘造影劑而發生過敏的病患上。此等反應無法以碘反應試驗或 其他現行可用的試驗預先得知。

急救設備應置於觸手可及處, 以備嚴重反應發生時之處置. 數種機轉可用於解釋此類反應

- 直接毒性反應影響血管內皮及組織蛋白.
- 藥理作用使部份內生因子濃度產生變化(組織胺, 補素, 發炎介質), 且觀察到在高滲透壓造影劑 發生頻率較高.
- 因Xenetix 使IgE 引發立即性過敏反應(過敏性反應)
- 因細胞機轉產生的過敏反應(延遲性皮膚過敏反應)

含碘造影劑及甲狀腺

給與含碘造影劑前, 應先確認病人不會接受甲狀腺閃爍掃描檢查(scintigraphic examination)或放射性碘治療. 投與含碘造影劑會干擾體內荷爾蒙濃度及影響甲狀腺或甲狀腺癌對碘 的吸收，直到尿液中碘回復正常.

其他警告

外滲(extravasation)是一種靜脈注射造影劑不常發生的併發症， 較常見 於高滲透壓造影劑。 而多數傷害為輕微, 嚴重的情況如皮膚潰瘍,組織 壞死,及腔室症侯群(compartment syndrome)可見於任何含碘造影劑。 其風險及/或嚴重度與病人相關(不良或脆弱的血管狀況）、及技術相關 (使用動力注射器, 大劑量)，重要的是辨認這些因子, 找到適合的注射 部位及運用技巧, 並於注射Xenetix的前,中,後加以監測。

使用注意事項

對含碘造影劑不耐症

檢查前:

- 根據病史篩檢確認高風險的病人. 對含碘造影劑不耐病史者，有建議以類固醇及H1-抗組織胺作預防 性投藥，但是無法預防嚴重或致命的過敏性休克之發生，檢查過程 中應採取下列措施 :
- 醫療監測
- 保留靜脈注射管線.

檢查後:

- 投與含碘造影劑後,應監測病人至少30分鐘,因為多數嚴重副作用發生於此時間內 ，應告知病人副作用可能會延遲至檢查後7天出現 。(見 4.8. 不良反應)

腎功能不全

含碘造影劑可誘發暫時性腎功能變化或使已存在的腎功能不全惡化，預防措施如下 :

- 確認高風險的病人, 即檢視是否病人有脫水或腎功能不全,糖尿病,嚴重心 衰竭,單株球蛋白症 (多發性骨髓瘤, Waldenstrom’s 巨球蛋白血症), 給與含 碘造影劑後產生腎衰竭的病史, 1歲以下孩童及有移瘤的年長者.
- 必要時以生理食鹽水補充水份.
- 避免與腎毒性藥物併用. 如果必須併用該類藥物, 則應加強腎功 能監測. 此類藥品包括氨基糖苷類抗生素 (aminoglycosides), 有機 鉑化合物 (organoplatinums), 高劑量氨甲喋呤 (methotrexate), 噴他 脒 (pentamidine), 膦甲酸鈉 (foscarnet), 某些抗病毒藥物 [acyclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], 萬古黴素 vancomycin, amphotericin B, 免疫抑製劑如環孢素 cyclosporine, tacrolimus, 及ifosfamide.
- 須注射含碘造影劑的兩個放射性檢查之間應至少間隔48小時, 或推遲 第二次檢查直到腎功能恢復至基線.
- 監看血清肌酸酐, 避免以metformin 治療的糖尿病因腎衰竭造成乳酸性 酸中毒.
- 腎功能正常 : 注射造影劑前48小時停止metformin 治療, 並於注射造影 劑後暫停服藥至少48小時, 或至腎功能已經恢復到基線後才能再度使 用metformin.
- 腎功能異常 : metformin 禁用.
- 在緊急情況下, 如果檢查是必要的, 要採取預防措施, 即停用metformin, 補充水份, 監測腎功能, 及檢測是否有乳酸性酸中毒的跡象. 含碘造影劑可用於血液透析的病人,因該等藥物可由血液透析移除. 使 用前應由血液透析科部核准.

肝功能不全

對於肝腎功能皆不全的病人應特別注意,因為會增加對造影劑的風險. 對於肝或腎功能不全的病人糖尿病病人或鐮狀細胞病病人要小心. 病人給與造影劑的前後, 尤其是對腎功能不全或糖尿病病人要確實補 充水份,以降低腎功能的減退.

氣喘

注射含碘造影劑前，確認氣喘患者為穩定狀態是必要的.

檢查前8日內曾有氣喘發作者, 應特別注意其支氣管痙攣風險增加.

甲狀腺功能異常

注射含碘造影劑後，尤其是甲狀腺腫的病人或有甲狀腺功能異常病史者, 有甲狀腺機能亢進發作或發生甲狀腺機能低下的風險, 新生兒或其母親接受含碘造影劑後,該新生兒有發生甲狀腺機能低下的風險。

心血管疾病 (見 4.8. 不良反應)

有心血管疾病的病人 (例如心衰竭, 冠狀動脈病變, 肺動脈高血壓, 瓣膜 病變, 心律不整), 注射含碘造影劑後的心血管風險增加。 靜脈注射含 碘造影劑後, 可能於初期心衰竭的病人引發肺水腫, 而在肺動脈高血壓 及瓣膜病變的病人可能導致血液動力學顯著變化。 其頻率及嚴重程 度與心臟疾病的嚴重度相關。 在嚴重高血壓患者， 注射含碘造影劑 及插入導管所導致的腎損傷風險可能增加，對這類病人謹慎評估臨床 利益/風險是必要的。

中樞神經系統疾病

以下患者使用本品應謹慎評估臨床利益/風險 :

- 在短暫性腦缺血發作、急性腦梗塞、近期齲內出血、腦水腫、或原發 或次發(腫瘤, 疤痕)癲癇患者，具有神經症狀惡化的風險。
- 當由動脈內給藥於嗜酒病人(急性或慢性酗酒)及其他藥癮者時.

嗜鉻細胞瘤

有嗜鉻細胞瘤的病人,於注射含碘造影劑後可發生高血壓危象,因此在檢查前須監測.

重症肌無力症

注射含碘造影劑後可加重重症肌無力症的症狀.

副作用的加重

注射含碘造影劑後可能加重患者煩燥不安、焦慮或疼痛等症狀，可能 須要適當的處置如鎮靜劑.

賦形劑

本產品含鈉. 其含量低於每100毫升1 mmol (23mg)。

4.5.與其他藥物的交互作用與其他形式的交互作用

避免數種併用藥物間發生交互作用, 應告知醫師或藥師目前正在進 行的治療

4.5.1. Medicinal products

+ 糖尿病用的Metformin (見4.4 節 使用特別注意事項一 腎功能不全).

+ 放射性藥物 (見4.4 節 警語)

碘造影劑會改變甲狀腺對於具放射活性的碘的吸收, 影響可達數週, 會降低閃爍掃描時的吸收，也降低碘 131的治療效果於排定進行腎臟閃爍掃描的病人並注射具放射活性且由腎小管排除的藥物，最好在注射含碘造影劑前先進行此項檢查

+ ß –受體阻斷劑, 血管收縮物質, 血管緊張素轉換酶抑制劑, 血管緊張素受體拮抗劑.

這些藥物降低對血壓失調的心血管補償機制效果: 醫師在投予含碘造影劑之前須了解此事, 並備妥緊急處置的方案.

+利尿劑

由於利尿劑容易引起脫水, 尤其使用高劑量的含碘造影劑時更容易發生，因此檢查前應補充水份及電解質以降低急性腎衰竭的風險.

+白細胞介素II

近期曾接受白細胞介素II 投藥（靜脈路徑）的病人, 對造影劑有反應的 風險增加 : 即皮疹, 或較罕見如低血壓, 少尿, 或甚至腎衰竭.

4.5.2. 其他形式的交互作用

高濃度含碘造影劑可影響體外血漿及尿液中膽紅素蛋白質及無機物(鐵, 銅, 鈣 ,和 磷)的測定. 建議不要在檢驗後24小時內進行上述物質的測定。

4.6.懷孕和授乳

胚胎毒性

動物實驗並未顯示致畸胎作用.

由於對不同動物品系的實驗並未顯示致畸胎作用，推論在人類亦同。至今會造成人類畸形的物質通常會在執行2種合適的動物實驗顯示致畸胎作用。

胎兒毒性

在超過14週無月經情形投藥於母親會導致暫時性碘過量，可能引發胎兒 甲狀腺功能異常. 然而在此作用為可逆且如果單獨注射含碘造影劑對懷 孕母親的檢查有益並經過小心評估後，則可在經上述考量下投於孕婦。

突變及生殖力

在實驗條件下本品未發現會導致突變。

無生殖功能相關的資料可獲得。

哺乳

含碘造影劑僅少量分泌於母乳中。單獨對母親給藥後對嬰兒有輕微的 風險, 因此建議注射含碘造影劑後停止哺乳24小時。

4.7.對開車和操作機器能力的影響

不適用.

4.8.不良反應

於905位病人進行的臨床試驗發現, 11%發生與Xenetix (溫熱感除外)有 關的副作用. 最常見的是疼痛, 注射部位疼痛, 味覺不良及噁心。副作用一般為輕至中度, 且為暫時性. 上市至今最常見的副作用是溫熱感, 注射部位疼痛和水腫。 過敏反應通常為立即發生(注射中或注射後一小時), 有時可為延遲 (注 射後一小時至數日), 以皮膚反應表現立即反應(immediate reactions)可由一或數個連續或同時發生的反應組 成, 通常包括皮膚反應, 呼吸道 及/或 心血管損傷, 可能是休克的第一徵 兆, 極少數會致命.

極罕有心臟疾病的病人發生嚴重的節律性異常,包括心室纖維顫動(ventricular fibrillation)報告 (見4.4 使用注意事項)。 不良反應在下表中以器官系統分類, 並依發生頻率表示如下 : 非常常見 (≥1/10), 常見 (≥1/100, <1/10), 不常見(≥1/1000, <1/100), 罕見 (≥1/10000, <1/1000), 非常罕見 (<1/10000), 未知 (依現有的資料, 無法估計). 頻率是 由觀察352,255位病人的試驗中取得。

器官系統分類	發生頻率	不良反應
免疫系統疾病	罕見	過敏症(hypersensitivity)
	非常罕見	類過敏性反應(anaphylactoid reaction), 過敏 性反應(anaphylactic reaction)
內分泌疾病	非常罕見	甲狀腺疾病
神經系統疾病	罕見 :	昏厥前兆 (迷走神經反應), 震顫*, 感覺異常*
	非常罕見	昏迷*, 抽搐*, 混亂*, 視力異常*,失憶*,畏光*, 暫時失明*,嗜眠*,不安*,頭痛
耳朵與內耳 迷路疾病	罕見	眩暈 聽力受損
心臟疾病	罕見	心跳加速
	非常罕見	心臟停止, 心肌梗塞(較常發生於冠狀動脈 內注射後), 心律不整, 心室纖維顫動, 心絞 痛
血管疾病	罕見	低血壓
	非常罕見	循環衰竭(circulatory collapse)
呼吸, 胸與縱隔疾病	罕見	呼吸困難, 咳嗽, 喉嚨緊感, 嗆嗆
	非常罕見	呼吸停止, 肺水腫, 支氣管痙攣, 喉部痙攣, 咽部水腫
胃腸道疾病	不常見	噁心
	罕見	嘔吐
	非常罕見	腹痛
皮膚及皮下組織疾病	罕見	血管性水腫, 蕁麻疹(局部 或廣泛), 紅斑, 搔癢
	非常罕見	急性泛發性發疹性膿皰病, Stevens-Johnson syndrome, Lyell’s syndrome, 濕疹, 斑丘疹 (皆屬延遲過敏反應)
腎臟及泌尿疾病	非常罕見	急性腎衰竭, 無尿
一般性疾病和給藥部位狀況	不常見	熱感
	罕見	臉腫, 倦怠, 畏寒,注射部位疼痛
	非常罕見	注射部位外滲後壞死, 注射部位水腫, 注射 部位外滲後發炎
實驗室檢驗數據	非常罕見	血液肌酸酐值上升

*檢查時大腦動脈血中的含碘造影劑濃度高

下列副作用曾出現於使用其他水溶性含碘造影劑的報告.

器官系統分類	不良反應
神經系統疾病	麻痺,局部麻痺,幻覺,言語障礙
胃腸道疾病	急性胰臟炎(ERCP後), 腹痛, 腹瀉, 腮腺 腫大, 唾腺分泌增加, 味覺障礙
皮膚及皮下組織疾病	多形性紅斑
一般性疾病和給藥部位狀況	血栓靜脈炎
實驗室檢驗數據	腦電圖異常, 血液澱粉酶值上升

不同嚴重度的心血管衰竭可能無預警的立即發生, 或使上表中心血管表現複雜化.

腹痛及腹瀉報告, 主要與口服或直腸給藥有關. 局部疼痛及水腫可發生於無外滲的注射部位, 可為良性且暫時的 動脈給藥時, 注射部位的疼痛感與注射藥品的滲透壓有關.

兒童

不良反應預期與成人報告相同. 其發生頻率依現有的資料, 無法估計.

4.9.過量

如果給藥劑量很高, 必須補充水份及電解質的流失，必須監測腎功能至少三天, 必要時進行血液透析。

5.藥理特性

5.1.藥效學性質

含碘造影劑

ATC代碼 : V08AB11 (V: 其他)

Xenetix 350 是一種用於泌尿道及血管攝影, 水溶性非離子造影劑, 其滲 透壓為 915 mOsm/kg.

5.2.藥物動力學特性

靜脈注射後, iobitridol 主要分佈於血管系統及細胞外液. 在人類之清除半衰期 是1.8小時. 分佈容量為200 mL/kg而清除率為93 mL/min (平均值). 血漿白蛋白 結合可忽略(< 2%). 主要經由腎臟以原型排除(腎丸球過濾而無腎小球再吸收 或分泌). Xenetix 350 引起的滲透性利尿作用視滲透壓及注射的劑量而定. 腎功能不全的病人, 主要經由膽汁排除. 本物可由透析清除.

5.3.臨床前安全性數據

靜脈注射無顯示毒性作用, 或毒性作用須較臨床使用建議情形更極端時才發生(劑量, 重覆給藥). 單次高劑量給藥(9 to 18 gI/kg)後Xenetix 引 起暫時性體溫降低, 呼吸抑制, 與作用器官發生劑量相關的組織損傷(肝臟, 腎臟), 及肝細胞空泡化、腎小管空泡化及膨脹. 對狗重覆高劑量給 藥(2.8 gI/kg)後. 觀察到停藥後具可逆性的粒狀的空泡退化. 局部刺激可於靜脈注射後發生外滲時觀察到. 動物的實驗並未顯示具致畸胎作用.

6.藥物特性

6.1.賦形劑清單

Edetate calcium disodium, trometamol, trometamol hydrochloride, sodium hydroxide 或 hydrochloric acid, 注射用水.

6.2.不相容性

由於缺乏相容性研究, 本品不應與其他藥品混合.

6.3.架貯期

3年 Three years.

6.4.儲存特別注意事項

小瓶 /瓶: 儲存溫度不可高於30°C, 避光.

6.5.容器的性質和內含物

50 mL, 100 mL, 200 mL 或 500 mL II 型玻璃小瓶 /瓶以chlorobutyl 橡皮 塞封閉.

6.6.丟棄與其它處理的注意事項

無特殊需求

7.上市許可持有者

GUERBET

16-24 RUE JEAN CHAPTAL

93600 AULNAY-SOUS-BOIS FRANCE

(POST BOX):BP 57400 - 95943 ROISSY CDG CEDEX FRANCE

許可證字號：衛署藥輸字第023931號

批號：請詳見外包裝

製造日期及有效日期：請詳見外包裝

製造廠名稱：Guerbet

製造廠地址：16-24 RUE JEAN CHAPTAL

93600 AULNAY-SOUS-BOIS, FRANCE

(POST BOX):BP 57400 - 95943 ROISSY CDG CEDEX FRANCE

藥商名稱：台灣古爾貝特股份有限公司

藥商地址：台北市中山區八德路二段182號

藥商電話：02-8773-0899

Guerbet

XENETIX® 350 INJECTION

1. NAME OF THE MEDICINAL PRODUCT
XENETIX 350 (350 mg Iodine/mL), solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Per 100 mL of solution:
Iobitridol ..... 76.78 g (767.8 mg/mL)
corresponding mass of iodine ..... 35 g (350 mg/mL)

- Iodine content per mL: 350 mg
- Viscosity at 20° C: 21 mPa.s
- Viscosity at 37° C: 10 mPa.s
- Osmolality: 915 mOsm/kg H_2O
- Iodine quantity per 50 mL vial: 17.5 g
- Iodine quantity per 100 mL vial: 35 g
- Iodine quantity per 200 mL bottles: 70 g
- Iodine quantity per 500 mL bottles: 175 g

Excipient with known effect: sodium (up to 3.5 mg per 100 mL).
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
This medicinal product is for diagnostic use only. Contrast agent for use in:
- Intravenous urography
- computed tomography
- intravenous digital subtraction angiography
- arteriography
- angiocardiography

4.2. Posology and method of administration
The doses must be adapted to the examination and to the regions of interest as well as to the body weight and renal function of the subject, particularly in children.

Recommended mean dosages:

Indications	Mean dose (mL/kg)	Total volume range (mL)
Intravenous urography:	1.0	50-100
CT:		
- cranial	1.0	40-100
- whole body	1.8	90-180
Intravenous digital subtraction angiography	2.1	95-250
Arteriography:		
- peripheral	2.2	105-205
- lower limbs	1.8	80-190
- abdominal	3.6	155-330
Angiocardiography		
- adults	1.9	65-270
- children	4.6	10-130

4.3.Contraindications
- Hypersensitivity to iobitridol or any of the excipients.
- History of a major immediate reaction or delayed skin reaction (see Section 4.8) to a Xenetix 350 injection.
- Manifest thyrotoxicosis

4.4.Special warnings and special precautions for use
- There is a risk of allergic reactions regardless of the route of administration or the dose.
- The risk of allergic reactions associated with products administered locally for opacification of body cavities is not clear-cut:

a) Administration via certain specific routes (articular, biliary, intrathecal, intra-uterine, etc.) results in varying degrees of systemic diffusion, i.e. systemic effects may be observed.
b) Oral or rectal administration normally results in very limited systemic diffusion. If the intestinal mucosa is normal, not more than 5% of the administered dose is found in urine and the rest is eliminated in faeces. Conversely, absorption is increased if the mucosa is damaged. In the event of perforation, this absorption is rapid and total with diffusion into the peritoneal cavity and the product is eliminated in urine. The occurrence of dose-dependent systemic effects is therefore dependent on the status of the intestinal mucosa.
c) However, the allergic immune mechanism is not dose-dependent and immuno-allergic reactions may occur at any time, regardless of the administration route.

Thus, in terms of the frequency and intensity of undesirable effects, there is a difference between:
- products administered via the vascular route and certain local routes, and
- products administered via the GI tract which are only slightly absorbed under normal conditions.

4.4.1. General particulars corresponding to all iodinated contrast agents
4.4.1.1 Warnings
In the absence of specific studies, myelography is not an indication for Xenetix.
All iodinated contrast agents can cause minor or major reactions that can be life-threatening. They may occur immediately (within 60 minutes) or be delayed (up to 7 days). They are often unpredictable.
Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use.
Several mechanisms have been evoked to explain the occurrence of these reactions:
- direct toxicity affecting the vascular endothelium and tissue proteins.
- pharmacological action modifying the concentration of certain endogenous factors (histamine, complement factors, inflammation mediators), observed more frequently with hyperosmolar contrast media.
- immediate IgE-mediated allergic reactions to the contrast agent Xenetix (anaphylaxis)
- allergic reactions due to a cellular-type mechanism (delayed cutaneous reactions)

Patients who have already experienced a reaction during administration of an iodinated contrast agent are at higher risk of experiencing another reaction following administration of the same or possibly a different iodinated contrast agent, and are thus considered to be at-risk patients.

Before administering an iodinated contrast agent, it is important to ensure that the patient is not scheduled to undergo a scintigraphic examination or laboratory tests related to the thyroid or to receive radioactive iodine for therapeutic purposes.
Administration of contrast agents via any route disrupts hormone concentrations and iodine uptake by the thyroid or by metastases of thyroid cancer, until urine iodine levels have returned to normal.

Other warnings
Extravasation is an unfrequent complication (0.04% to 0.9%) of intravenous injections of contrast media. More frequent with the high osmolar products, most of the injuries are minor, however severe injuries such as skin ulceration, tissue necrosis, and compartment syndrome may occur with any iodinated contrast medium. The risk and/or severity factors are patient-related (poor or fragile vascular conditions), and technique-related (use of a power injector, large volume). It is important to identify these factors, optimize the injection site and technique accordingly, and monitor the injection prior to, during and after the injection of Xenetix.

4.4.1.2. Precautions for use
4.4.1.2.1. Intolerance to iodinated contrast agents:
Prior to the examination:
- identify at-risk patients by a precise screening of histories.

Corticosteroids and H1-type antihistamines have been suggested as premedication in patients presenting with the highest risk for intolerance reactions (history of intolerance to an iodinated contrast agent). However, they do not prevent the occurrence of serious or fatal anaphylactic shock. During the procedure, the following measures must be maintained:
- medical surveillance
- permanent venous access.

After the examination:
- After administration of the contrast agent, the patient must be monitored for at least 30 minutes, since most serious adverse reactions occur within this time period.
- The patient must be informed of the possibility of delayed reactions (for up to seven days) (see Section 4.8. Undesirable effects)

4.4.1.2.2. Renal insufficiency
Iodinated contrast agents can induce a transient alteration in renal function or worsen pre-existing
renal insufficiency. Preventive measures include:
- Identify at-risk patients, i.e. with dehydration or renal insufficiency, diabetes, severe heart failure, monoclonal gammapathy (multiple myeloma, Waldenstrom's macroglobulinemia), a history of renal failure after iodinated contrast agent administration, children under one year of age and elderly subjects with atheroma.
- Hydrate when necessary using a saline solution.
- Avoid combinations with nephrotoxic medicines. If this cannot be avoided, laboratory monitoring of renal function must be intensified. The medicines concerned include aminoglycosides, organoplatinum compounds, high doses of methotrexate, pentamidine, foscarnet and certain antiviral agents [aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], vancomycin, amphotericin B, immunosuppressants such as cyclosporine or tacrolimus, ifosfamide)
- Allow at least 48 hours between two radiological examinations with injection of contrast agents, or postpone any new examination until renal function returns to baseline.
- Prevent lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine levels. Normal renal function: treatment with metformin must be suspended before contrast agent injection and for at least 48 hours after or until normal renal function is restored. Abnormal renal function: metformin is contraindicated. In case of emergency: if the examination is mandatory, precautions must be taken, i.e. metformin discontinuation, hydration, monitoring of renal function and checking for signs of lactic acidosis.

Iodinated contrast agents can be used in haemodialysed patients as the agents are removed by dialysis. Prior approval should be obtained from the haemodialysis department.

4.4.1.2.3. Hepatic insufficiency
Particular attention is required when a patient presents with both hepatic and renal insufficiency since, in this situation, the risk of contrast agent retention is increased.
Care should be taken in case of renal or hepatic impairment, diabetes or in patients with sickle cell disease.
Adequate hydration should be ensured in all patients before and after contrast media administration and particularly in patients with renal impairment or diabetes where it is important to maintain hydration to minimise deterioration in renal function.

4.4.1.2.4. Asthma
Stabilisation of asthma is recommended before the injection of an iodinated contrast agent.
Due to an increased risk of bronchospasm, special caution should be taken in patients who suffered an asthmatic attack within eight days prior to the examination.

4.4.1.2.5. Dysthyroidism
After iodinated contrast agent injection, particularly in patients with a goitre or a history of dysthyroidism, there is a risk either of a flare-up of hyperthyroidism or development of hypothyroidism. There is also a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent.

4.4.1.2.6. Cardiovascular disorders (see Section 4.8. Undesirable effects)
In patients with cardiovascular disorders (such as early or patent heart failure, coronaropathy, pulmonary hypertension, valvulopathy, cardiac arrhythmias), the risk of cardiovascular reactions is increased after administration of an iodinated contrast agent. Intravascular injection of the contrast medium may cause pulmonary oedema in patients with manifest or incipient heart failure, whereas administration in pulmonary hypertension and heart valve disorders may result in marked changes in haemodynamics. The frequency and degree of severity appear related to the severity of the cardiac disorders. In case of severe and chronic hypertension, the risk of renal damage due to administration of the contrast medium and also due to the catheterisation itself may be increased. Careful weighing up of the risk-benefit ratio is necessary in these patients.

4.4.1.2.7. Central nervous system disorders
The benefit-to-risk ratio must be evaluated for each case:
- due to the risk of aggravation of neurological symptoms in patients with a transient ischaemic attack, acute cerebral infarct, recent intracranial haemorrhage, cerebral oedema, or idiopathic or secondary (tumour, scar) epilepsy.
- if the intra-arterial route is used in an alcoholic patient (acute or chronic alcoholism) and other drug addicted subject.

4.4.1.2.8. Phaeochromocytoma
Patients with phaeochromocytoma may develop a hypertensive crisis after intravascular administration of a contrast agent, and must be monitored prior to the examination.

4.4.1.2.9. Myasthenia.
Administration of a contrast agent may worsen the symptoms of myasthenia gravis.

4.4.1.2.10. Intensification of side effects
Adverse reactions related to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety and pain. Appropriate management such as sedation may be necessary.

4.4.1.2.11. Excipients
This medicinal product contains sodium. It contains less than 1 mmol sodium per 100 mL, i.e. essentially "sodium-free".

4.5. Interaction with other medicinal products and other forms of interaction
In order to avoid any interaction between several concomitant drugs, you should always inform your physician or your pharmacist of any other on-going treatment:

4.5.1. Medicinal products
+ Metformin in diabetics (see Section 4.4 Precautions for use — renal insufficiency).
+ Radiopharmaceuticals (see Section 4.4 Warnings)
Iodinated contrast agents alter the uptake of radioactive iodine by the thyroid for several weeks, which may on the one hand result in diminished uptake in thyroid scintigraphy and on the other hand decrease the efficacy of iodine 131 treatment.

In patients scheduled to undergo renal scintigraphy with injection of a radiopharmaceutical excreted by the renal tubules, it is preferable to carry out this examination before injecting the iodinated contrast agent.
+ Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists.
These medicinal products reduce the efficacy of the cardiovascular compensation mechanisms that occur in haemodynamic disorders. The physician must be aware of this before injecting the iodinated contrast agent and appropriate intensive care equipment must be available.
+ Diuretics
Due to the risk of dehydration provoked by diuretics, rehydration with water and electrolytes must be carried out prior to the examination in order to limit the risk of acute renal failure.
+ Interleukin 2
The risk of developing a reaction to the contrast agents is increased if the patient has recently been treated with interleukin 2 (intravenous route), i.e. rash or, more rarely, hypotension, oliguria, or even renal failure.

4.5.2. Other forms of interaction
High concentrations of iodinated contrast agents in plasma and urine may interfere with the in vitro determination of bilirubin, proteins and inorganic substances (iron, copper, calcium and phosphate). It is recommended that these determinations should not be carried out within 24 hours following the examination.

4.6. Pregnancy and lactation
Embryotoxicity
Animal studies have not shown any teratogenic effects.
In the absence of any teratogenic effects in animal species, no malformative effect is expected in humans. To date, substances causing malformations in humans have always proved to be teratogenic in animals during studies properly conducted in two species.
Foetotoxicity
The transient iodine overload following administration to the mother may induce foetal dysthyroidism if the examination takes place after more than 14 weeks of amenorrhoea. However, in view of the reversibility of the effect and expected benefit to the mother, the isolated administration of an iodinated contrast agent is justifiable if the indication for the radiological examination in a pregnant woman has been carefully evaluated.

Mutagenicity and fertility
The product was not found to be mutagenic under the test conditions used. No data on reproductive function are available.
Lactation
Iodinated contrast agents are only excreted in breast milk in very small amounts. Isolated administration to the mother consequently involves a minor risk of adverse reactions in the infant. It is advisable to stop breastfeeding for 24 hours after administration of the iodinated contrast agent.

4.7. Effects on ability to drive and use machines
Not applicable.

4.8. Undesirable effects
During clinical studies on 905 patients, 11% of patients experienced an adverse reaction related to administration of Xenetix (apart from feeling of warmth), the most common being pain, injection site pain, bad taste and nausea.
Undesirable effects related to the use of Xenetix are generally mild to moderate, and transient.
The adverse reactions most commonly reported during administration of Xenetix since marketing are feeling of warmth, and pain and oedema at the injection site.
The hypersensitivity reactions are usually immediate (during the injection or over the hour following the start of the injection) or sometimes delayed (one hour to several days after the injection), and then appear in the form of adverse skin reactions.
Immediate reactions comprise one or several, successive or concomitant effects, usually including skin reactions, respiratory and/or cardiovascular disorders, which may be the first signs of shock, which can rarely be fatal.
Severe rhythm disorders including ventricular fibrillation have been very rarely reported in heart disease patients, in as well as out of a context of hypersensitivity (see Section 4.4 Precaution for use).
The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data). The frequencies presented are derived from the data of an observational study on 352,255 patients.

System Organ Class	Frequency: adverse reaction
Immune system disorders	Rare: hypersensitivity Very rare: anaphylactoid reaction, anaphylactic reaction
Endocrine disorders	Very rare: thyroid disorder
Nervous system disorders	Rare: presyncope (vasovagal reaction), tremor*, paresthesia* Very rare: coma*, convulsions*, confusion*, visual disorders*, amnesia*, photophobia*, transient blindness*, somnolence*, agitation*, headache
Ear and labyrinth disorders	Rare: vertigo Very rare: hearing impaired
Cardiac disorders	Rare: tachycardia Very rare: cardiac arrest, myocardial infarction (more frequent after intracoronary injection), arrhythmia, ventricular fibrillation, angina pectoris
Vascular disorders	Rare: hypotension Very rare: circulatory collapse
Respiratory, thoracic and mediastinal disorders	Rare: dyspnoea, cough, tightness in the throat, sneezing Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, laryngeal oedema
Gastrointestinal disorders	Uncommon: nausea Rare: vomiting Very rare: abdominal pain
Skin and subcutaneous tissue disorders	Rare: angioedema, urticaria (localised or extensive), erythema, pruritus Very rare: Acute Generalised Exanthematous Pustulosis, Stevens-Johnson syndrome, Lyell's syndrome, eczema, maculopapulous exanthema (all as delayed hypersensitivity reactions)
Renal and urinary disorders	Very rare: acute renal failure, anuria
General disorders and administration site conditions	Uncommon: feeling hot Rare: facial oedema, malaise, chills, injection site pain Very rare: injection site necrosis following extravasation, injection site oedema, injection site inflammation following extravasation
Investigations	Very rare: blood creatinine increased

*Examinations during which the iodinated contrast agent concentration in arterial blood is high.

The following adverse reactions were reported for other water-soluble iodinated contrast agents:

System Organ Class	Frequency: adverse reaction
Nervous system disorders	Paralysis, paresis, hallucinations, speech disorders
Gastrointestinal disorders	Acute pancreatitis (after ERCP), abdominal pain, diarrhoea, parotid gland enlargement, salivary hypersecretion, dysgeusia
Skin and subcutaneous tissue disorders	Erythema multiforme
Vascular disorders	Thrombophlebitis
Investigations	Electroencephalogram abnormal, blood amylase increased

Cardiovascular collapse of variable severity may occur immediately with no warning signs, or may complicate the cardiovascular manifestations mentioned in the above table.
Abdominal pain and diarrhoea, not reported for Xenetix, are linked mainly to administration via the oral or rectal route.
Local pain and oedema may occur at the injection site without extravasation of the injected product and are benign and transient.
During intra-arterial administration, the sensation of pain at the injection site depends on the osmolality of the product injected.

Paediatric population
The expected nature of the undesirable effects connected with Xenetix is the same as that of the effects reported in adults. Their frequency cannot be estimated from the available data.

4.9.Overdose
If a very high dose of contrast agent is administered, the water and electrolyte loss must be compensated by suitable rehydration. Renal function must be monitored for at least three days. Haemodialysis may be performed if necessary.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
IODINATED CONTRAST AGENT
(V: other) ATC code: V08AB11
Xenetix 350 is a urographic and angiographic water-soluble nonionic contrast agent with an osmolality of 915 mOsm/kg.

5.2. Pharmacokinetic properties
After intravascular injection, iobitridol is distributed in the intravascular system and interstitial compartment. In humans, the elimination half-life is 1.8 h, the volume of distribution is 200 mL/kg and the total clearance is 93 mL/min (mean values). Binding to plasma proteins is negligible (< 2%). It is mainly eliminated via the kidneys (glomerular filtration without tubular reabsorption or secretion) in unchanged form. The osmotic diuresis induced by Xenetix 350 is dependent on the osmolality and the volume injected. In patients with renal insufficiency, elimination occurs mainly via the biliary route. The substance can be dialysed.

5.3. Preclinical safety data
Toxicological results for intravenous use show an absence of effects, or effects occurring under conditions much more extreme than those recommended for clinical use (dosage, repeated doses). Following the single administration of high doses (9 to 18 gI/kg), Xenetix caused transient signs of hypothermia, respiratory depression and dose-dependent histological lesions that occurred in the target organs (liver, kidney) and included hepatocellular vacuolisation, and tubular vacuolisation and dilation. Following repeated administration of high doses (2.8 gI/kg) for 28 days in dogs, granular vacuolar degeneration that was reversible after discontinuation of treatment was observed.
Local irritation could be observed in the event of extravasation. Animal studies did not demonstrate any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Sodium calcium edetate, trometamol, trometamol hydrochloride, sodium hydroxide or hydrochloric acid, water for injection.

6.2.Incompatibilities
In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life
Three years.

6.4. Special precautions for storage
Vials/bottles: Do not store above 30°C, store protected from light.

6.5. Nature and content of container
50 mL, 100 mL, 200 mL or 500 mL type II glass vials/bottles with chlorobutyl rubber stoppers. Not all pack sizes may be marketed.

6.6. Instructions for disposal and handling
No special requirements

7. MARKETING AUTHORISATION HOLDER
GUERBET BP 57400
F-95943 Roissy CDG Cedex
FRANCE

GUERBET
16-24 RUE JEAN CHAPTAL
93600 AULNAY-SOUS-BOIS FRANCE
(POST BOX):BP 57400 95943 ROISSY CDG CEDEX
FRANCE

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