孕保寧 注射劑

衛署藥輸字第 024562 號

TRACTOCILE® solution for injection 7.5 mg/ml

孕保寧 濃縮輸注液

衛署藥輸字第 024561 號

TRACTOCILE® concentrate for solution for infusion 7.5 mg/ml

【組成】
注射劑：每毫升的溶液含有 7.5 毫克的 atosiban
濃縮輸注液：每毫升的溶液含有 7.5 毫克的 atosiban
在根據配製方法稀釋後 atosiban 濃度是 0.75mg/ml.
賦形劑：Mannitol, hydrochloric acid 1M and water for injections

【藥物劑型】
注射劑：每小瓶（0.9ml）含 6.75 毫克
濃縮輸注液：每小瓶（5ml）含 37.5 毫克

【適應症】
延遲妊娠婦女迫切的早產。
說明：
TRACTOCILE® 用於延遲以下妊娠婦女迫切的早產：
- 規律宮縮至少持續 30 秒，頻率大於等於每 30 分鐘 4 次
- 宮頸擴張 1-3 公分（未經產婦 0-3 公分）和宮頸展平大於等於 50%
- 年齡大於等於 18 歲
- 孕齡在 24-33 周
- 胎兒心率正常

【用法用量】
本藥限由醫師使用
TRACTOCILE® 治療的開始及維持應由有治療早產經驗的醫生進行。
早產一經診斷，建議儘早開始初始靜脈推注。一旦靜脈推注已注射，隨後立即給予輸注。
靜脈給予 TRACTOCILE® 分為三個階段：初始以 TRACTOCILE® 7.5 mg/ml 注射劑靜脈推注 6.75 毫克劑量；隨後立即給予 3 小時持續的大劑量輸注 TRACTOCILE® 7.5 mg/ml 輸注用濃縮液（負荷劑量滴注 300 微克 / 分鐘）；續以小劑量輸注 TRACTOCILE® 7.5 mg/ml 濃縮輸注液（後續劑量滴注 100 微克 / 分鐘），最長持續 45 小時。治療時間不能超過 48 小時，整個療程 TRACTOCILE® 的總劑量最好不要超過 330 毫克（以 atosiban 計）。
如果在 TRACTOCILE® 治療期間，子宮仍持續收縮，應考慮其他替代療法。
對腎功能或肝功能不全的婦女使用 TRACTOCILE® 治療是否需要調整劑量，目前尚無資料。
下表顯示靜脈推注隨後立即給予輸注的劑量：

階段	給藥方式	速　率	劑　量
1	0.9 毫升靜脈注射	超過 1 分鐘	6.75 毫克
2	3 小時靜脈滴注	24 毫升 / 小時	18 毫克 / 小時
3	靜脈滴注	8 毫升 / 小時	6 毫克 / 小時

再次治療：
如果需要以 TRACTOCILE® 再次治療，也要先開始以 TRACTOCILE® 7.5 mg/ml 注射劑靜脈推注，接著再以 TRACTOCILE® 7.5 mg/ml 輸注用濃縮液給予輸注。

【禁忌】
在以下情況下不要使用 TRACTOCILE®：
- 懷孕週數不足 24 週或超過 33 週
- 早期破水且懷孕週數大於 30 週
- 宮內發育遲緩及胎兒心率不正常
- 分娩前子宮出血需要立即分娩
- 子癇或嚴重的先兆子癇需要分娩
- 胎兒宮內死亡
- 懷疑宮內感染
- 前置胎盤
- 胎盤早剝
- 任何繼續妊娠對母親和胎兒有害的情況
- 對藥物或任何一種賦形劑過敏

【警語及注意事項】
當 atosiban 使用在不能排除有早期破水的病人時，需權衡延遲分娩的益處及發生絨毛膜羊膜炎的潛在危險性。
對腎功能或肝功能不全的婦女使用 atosiban 治療還缺乏經驗（見劑量及給藥方式與藥物動力學性質）。
Atosiban 未曾使用在胎位不正的病人。
Atosiban 使用於多胎妊娠或是懷孕週數介於 24 至 27 週的早產婦女的臨床經驗非常有限，因為此類病患人數少 TRACTOCILE® 對於這些子群的益處並不確定。
以 TRACTOCILE® 再次治療是可能的。但是對於多次治療的臨床經驗非常有限，最多只有三次的再治療（見劑量及給藥方式）。
對於子宮發育遲緩的婦女，決定是否繼續或是重新開始 TRACTOCILE® 治療主要依賴對胎兒成熟度的評估。
在使用 atosiban 期間建議定期監測母親的子宮收縮及胎兒心率，且應該考慮到發生持續宮縮的可能。
作為催產素拮抗劑，atosiban 理論上能夠有利於子宮舒張以及產後出血。因此應監測分娩後的失血量。然而在臨床試驗中沒有觀察到產後子宮收縮乏力。
多胎妊娠和抑制子宮收縮（tocolytic activity）的藥品，例如：鈣離子阻斷劑和 beta-mimetics 已知會增加肺水腫的風險。因此如果有多胎妊娠和 / 或同時使用其他子宮鬆弛劑時，應該小心使用 atosiban。

【與其它的醫藥產品的交互作用及其它形式的交互作用】
體外試驗顯示 atosiban 不是 Cytochrome P450 系統的受質，而且也不會抑制代謝藥物的 Cytochrome P450 的酵素。因此 atosiban 不可能牽涉到 Cytochrome P450 所媒介的藥物 - 藥物交互作用。
在健康女性的志願受試者執行 atosiban 與 betamethasone 及 labetalol 交互作用的研究。Atosiban 與 betamethasone 沒有臨床上相關的交互作用。當 atosiban 與 labetalol 同時使用時，labetalol 的 C_{max} 減少 36%，T_{max} 延長 45 分鐘。然而以 AUC 來看的生體可用率不變。這個觀察到交互作用並沒有臨床上的相關性。Labetalol 不會影響 atosiban 的藥物動力學。
與抗生素、麥角鹼以及非 labetalol 的抗高血壓藥物沒有交互作用方面的研究。

【妊娠及哺乳】
Atosiban 只能用於懷孕週數在 24-33 週妊娠婦女的早產。
在 atosiban 臨床試驗中，沒有觀察到對哺乳的影響。已經證明少量 atosiban 從哺乳婦女的血漿進入乳汁中。
在胚胎毒性研究中還沒有 atosiban 毒性作用的報告。沒有包括受孕和早期胚胎發育的實驗被執行（見臨床前的安全性資料）。

【副作用】
臨床試驗使用 atosiban 的母親可能發生的副作用已被描述。觀察到的副作用一般為輕微的。
48%以 atosiban 治療的病人曾經驗到副作用。
臨床試驗沒有發現 atosiban 對新生兒有任何副作用，胎兒的不良事件均在正常變異範圍內，且與安慰劑組及 ß- 受體促進劑組是相似的。
在婦女的副作用如下：

MedDRA 系統分類	非常常見（≥ 10%）	常見（≥ 1- <10%）	不常見（≥ 0.1- <1%）	罕見（≥ 0.01- <0.1%）
免疫系統				過敏
代謝和營養系統		血糖升高		
精神系統			失眠	
神經系統		頭痛、頭暈		
心臟系統		心跳過速		
血管系統		低血壓		
胃腸道系統	噁心			
皮膚及皮下組織系統			搔癢、皮疹	
生殖和乳房系統				子宮出血、子宮乏力
一般疾病和投予部位反應		潮紅、注射部位反應	發燒	

上市後曾有呼吸系統不良事件的報告如呼吸困難和肺水腫，特別是同時使用其他抑制子宮收縮的藥品如鈣離子拮抗劑和 beta-mimetics 和 / 或多胎妊娠時。

【藥物過量】
有幾例使用 atosiban 過量的報告，但這些病例都沒有特殊的症狀。對藥物過量沒有已知的特定療法。

藥理性質

【藥效學性質】
藥物治療分類：其他婦科，ATC 代碼：G02CX01
TRACTOCILE® 的成分為 atosiban，是一種合成的胜肽類。化學名為 1-（3-硫醇丙醇酸）-2-（O- 乙基 -D- 酪氨酸）-4-L- 蘇氨酸 -8-L- 鳥氨酸 - 催產素。
atosiban 是一個競爭性催產素受體拮抗劑。在老鼠及天竺鼠，atosiban 與催產素受體結合，減少收縮的頻率以及子宮肌層的張力，而抑制了子宮的收縮。
atosiban 也會與血管加壓素受體結合，因此抑制血管加壓素的作用。atosiban 在動物沒有顯現心臟血管的作用。
在人類的早產，atosiban 在建議劑量下可拮抗子宮的收縮而誘導子宮靜止。給予 Atosiban 後，子宮放鬆的開始作用時間很快，子宮收縮在 10 分鐘內可顯著的減少，而達到持續 12 小時穩定的子宮靜止（≤ 4 次收縮 / 小時）。
III 期臨床試驗（CAP-001）研究，共有 742 名孕齡介於 23 至 33 周的早產婦女。隨機給予 atosiban（依照仿單使用）或是 ß- 受體促進劑（調整劑量）。
主要療效指標：主要的效力結果是從治療開始 7 天內未分娩且不需要其他保胎藥治療的婦女比例。治療 7 天內未分娩且不需要其他保胎藥治療的婦女比例：TRACTOCILE® 組為 59.6%（n=201）；ß- 受體促進劑組為 47.7%（n=163, p=0.0004）。在 CAP-001 研究中，大部分的治療失敗是由於耐受性不好所造成。TRACTOCILE® 組中因為治療效力不足夠所造成的治療失敗的頻率（n=48, 14.2%）明顯（p=0.0003）高於 ß- 受體促進劑組（n=20, 5.8%）。
在 CAP-001 研究中，孕齡介於 24 至 28 周的早產婦女，治療 7 天內未分娩且不需要其他保胎藥治療的機率，atosiban 組和 ß- 受體促進劑組是類似的。不過這個發現是基礎在非常少的樣本（n=129 病人）。
次要療效指標：次要效力變數包括治療開始 48 小時內未分娩的婦女比例。對於這個變數，Atosiban 組和 ß- 受體促進劑組並無差異。
兩組分娩時的平均孕齡是相同的（p=0.37），atosiban 組為 35.9（3.9）周，ß- 受體促進劑組為 35.3（4.2）周。
在新生兒加護病房停留的天數和使用呼吸器治療兩組是類似的（大約 30%）。
Atosiban 組的平均出生體重為 2491（813）公克，ß- 受體促進劑組為 2461（831）公克（p=0.58）。
對於胎兒和母體的結果 atosiban 組和 ß- 受體促進劑劑組並沒有明顯的差異，不過臨床研究並沒有足夠的能力去排除可能的差異。
III 期臨床試驗，361 位接受 atosiban 治療的婦女中，有 73 位接受至少一次的再治療，有 8 位接受至少二次的再治療，有 2 位接受至少三次的再治療（見警語及注意事項）。
因為 atosiban 在孕齡不足 24 周的婦女上的安全性和療效尚未在對照隨機試驗建立，所以不建議以 atosiban 治療這個病人群（見禁忌）。
在一項安慰劑對照的試驗中，胎兒 / 嬰兒的死亡率在安慰劑組中是 5/295（1.7%），在 atosiban 組是 15/288（5.2%）。Atosiban 組有兩位是在五個月和八個月大時死亡。Atosiban 組中十五個死亡案例其中的十一個是在懷孕週數 20 至 24 週曝露於 atosiban 的婦女，雖然在這個子群中兩組病人的分佈是不相等的（19 個婦女在 atosiban 組，4 個婦女在安慰劑組）。對於懷孕週數大於 24 週的婦女，兩組的死亡率沒有差別（安慰劑組為 1.7%，atosiban 組為 1.5%）。

【藥物動力學性質】
健康的未孕婦女接受 atosiban 輸注（10-300 微克 / 分鐘，持續 12 小時），其穩定狀態的血漿濃度與劑量成等比例地增加。
清除率、分佈容積及半衰期與劑量無關。
早產的婦女接受 atosiban 輸注（10-300 微克 / 分鐘，持續 6-12 小時），在接受輸注後一小時內即達到穩定狀態的血漿濃度（平均濃度 442±73 ng/ml，298 至 533 ng/ml 範圍間）。
在輸注完成之後，血漿濃度很快的以起始半衰期（tα）0.21±0.01 小時及終端半衰期（tß）1.7±0.3 小時下降。平均清除率為 41.8±8.2 公升 / 小時，平均分佈容積為 18.3±6.8 公升。
在懷孕婦女 atosiban 的血漿蛋白結合率為 46%至 48%。母體與胎兒的未結合部分尚不知是否有很大的差異。Atosiban 不會分配到紅血球。
Atosiban 會通過胎盤。健康懷孕末期的婦女在輸注 atosiban 300 微克 / 分鐘後，胎兒 / 母體的 atosiban 濃度比為 0.12。
在人類的血漿及尿液中有兩個代謝物被鑑定出來。主要代謝物 M1（des-（Orn^8, $Gly\text{-}NH_2^9$）-[Mpa^1,D-Tyr（Et）^{2}, Thr^4]-oxytocin）的血漿濃度比上 atosiban 的血漿濃度的比例，在輸注的第二小時為 1.4；在輸注結束為 2.8。尚不知 M1 是否會積蓄在組織中。在尿液中只有非常少量的 atosiban 被發現；在尿液中 atosiban 的濃度大約比 M1 的濃度低 50 倍。尚不知有多少部分的 atosiban 是經由糞便排出。在體外主要代謝物 M1 抑制 oxytocin 所誘導的子宮收縮比 atosiban 大約小於 10 倍。代謝物 M1 會分泌到乳汁。（見妊娠及哺乳）
對腎功能或肝功能不全的婦女使用 TRACTOCILE® 治療還缺乏經驗。（見用法用量 與 警語及注意事項）
Atosiban 不會抑制肝臟 Cytochrome P450 的異酵素。（見與其它的醫藥產品的交互作用及其它形式的交互作用）

【臨床前的安全性資料】
在兩個星期的靜脈注射毒性試驗中（在老鼠與狗），投與比人類治療劑量高十倍的劑量；以及在老鼠與狗的三個月的毒性試驗中（20mg/kg/day 皮下注射），沒有觀察到全身性的毒性作用。
不會產生任何副作用的 atosiban 最高的皮下注射劑量大約是人類治療劑量的兩倍。
沒有包括受孕和胚胎早期發育的試驗被執行。生殖毒性試驗顯示對母親及胎兒沒有作用。老鼠胎兒所接受的劑量大約是人類胎兒的四倍。從抑制 oxytocin 的作用來預期，動物試驗顯示會抑制泌乳。
Atosiban 既沒有致癌性也不會導致突變。

【配伍禁忌】
缺乏配伍禁忌試驗，不可與其他藥物混合

【架儲期】
架儲期：4 年
注射劑：一旦開啟，必須立即使用。
濃縮輸注液：一旦開啟，必須立即稀釋。
供靜脈輸注之溶液稀釋後應在 24 小時內使用。

【儲存時的注意事項】
儲存在攝氏 2 至 8℃的環境
儲存在原來的容器內

使用操作說明

注射劑

使用前應先肉眼查看小瓶是否有微粒及變色，如有微粒及變色，應丟棄勿使用。
初始靜脈推注用溶液的準備：
從 0.9 毫升小瓶中抽取 TRACTOCILE® 7.5 毫克 / 毫升注射液 0.9 毫升，在產房有足夠的醫療監視下以靜脈推注的方式在大於一分鐘的時間緩慢給予。
TRACTOCILE® 7.5 毫克 / 毫升注射液在開啟後必須立即使用。
缺乏配伍禁忌試驗，不可與其他藥物混合（見配伍禁忌）

濃縮輸注液

使用前應先肉眼查看小瓶是否有微粒及變色，如有微粒及變色，應丟棄勿使用。。
靜脈輸注液的準備：
靜脈推注後，應靜脈滴注 7.5 毫克 / 毫升 TRACTOCILE® 濃縮輸注液，採用下列溶液之一稀釋：
- 0.9%（w/v）等張生理鹽水
- 林格氏乳酸溶液
- 5%（w/v）等張葡萄糖溶液

在 100 毫升輸液袋中準備藥物溶液時，從輸液袋中抽取 10 毫升液體棄掉，再抽取 10 毫升 7.5 毫克 / 毫升 TRACTOCILE® 輸注用濃縮液（兩個 5 毫升小瓶）注入其中，這樣 100 毫升液體中就含有 75 毫克 TRACTOCILE®。在產房有足夠的醫療監視下給予負荷劑量滴注每小時 24 毫升，相當於每小時 18 毫克，持續 3 小時。3 小時後降為每小時 8 毫升。
為了讓滴注持續不間斷，再按照上述的方法準備 100 毫升輸液袋。
如果輸液袋的體積不同，就要按比例計算配製相同濃度的輸液。
為確保劑量準確，建議使用一種可控制滴速的裝置，這樣可以控制流速到滴 / 分鐘。靜脈微滴室可以提供在 TRACTOCILE® 建議劑量範圍內的方便滴注速度。
缺乏配伍禁忌試驗，不可與其他藥物混合（見配伍禁忌）。如果其他藥物需同時靜脈給予時，可共用靜脈套管或是使用其他靜脈注射部位。這樣可允許連續獨立控制滴注速度。

製造廠：Ferring GmbH
廠　址：Wittland 11, D-24109 Kiel, Germany
包裝廠：Ferring International Center SA
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TRACTOCILE®

7.5 mg/ml solution for injection
7.5 mg/ml concentrate for solution for infusion

FERRING PHARMACEUTICALS

■ QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection

One ml solution contains 7.5 mg atosiban free base in the form of atosiban acetate.

Concentrate for solution for infusion

One ml solution contains 7.5 mg atosiban free base in the form of atosiban acetate.

After dilution according to the instructions in INSTRUCTIONS FOR USE AND HANDLING, the concentration of atosiban is 0.75 mg/ml.

■ Excipients: Mannitol, hydrochloric acid 1M and water for injections.

■ PHARMACEUTICAL FORM

Solution for injection

Solution for injection.Each vial contains 6.75 mg atosiban.

Concentrate for solution for infusion

Concentrate for solution for infusion. Each vial contains 37.5 mg atosiban.

■ THERAPEUTIC INDICATIONS

TRACTOCILE® is indicated to delay imminent preterm birth in pregnant women with:

- regular uterine contractions of at least 30 seconds duration at a rate of ≥ 4 per 30 minutes
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of ≥ 50%
- age ≥ 18 years
- a gestational age from 24 until 33 completed weeks
- a normal fetal heart rate

POSOLOGY AND METHOD OF ADMINISTRATION

Treatment with TRACTOCILE® should be initiated and maintained by a physician experienced in the treatment of preterm labour.

Intravenous therapy using the initial bolus injection of TRACTOCILE® 7.5 mg/ml, solution for injection, should be started as soon as possible after diagnosis of preterm labour. Once the bolus has been injected, proceed with the infusion.

TRACTOCILE® is administered intravenously in three successive stages: an initial bolus dose (6.75 mg), performed with TRACTOCILE® 7.5 mg/ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 µg/min) of TRACTOCILE® 7.5 mg/ml concentrate for solution for infusion during three hours, followed by a lower dose of TRACTOCILE® 7.5 mg/ml concentrate for solution for infusion (subsequent infusion 100 µg/min) up to 45 hours. The duration of the treatment should not exceed 48 hours. The total dose given during a full course of TRACTOCILE® therapy should preferably not exceed 330 mg of the active substance.

In the case of persistence of uterine contractions during treatment with TRACTOCILE®, alternative therapy should be considered.

There is no data available regarding the need for dose adjustments in patients with renal or liver insufficiency.

The following table shows the full posology of the bolus injection followed by the infusion:

Step	Regimen	Injection/infusion rate	Atosiban dose
1	0.9 ml intravenous bolus	over 1 minute	6.75 mg
2	3 hours intravenous loading infusion	24 ml/hour	18 mg/hour
3	subsequent intravenous infusion	8 ml/hour	6 mg/hour

Re-treatment

In case a re-treatment with TRACTOCILE® is needed, it should also commence with a bolus injection of TRACTOCILE® 7.5 mg/ml, solution for injection followed by infusion with TRACTOCILE® 7.5 mg/ml, concentrate for solution for infusion.

■ CONTRAINDICATIONS

TRACTOCILE® should not be used in the following conditions:

- Gestational age below 24 or over 33 completed weeks
- Premature rupture of the membranes > 30 weeks of gestation
- Intrauterine growth retardation and abnormal fetal heart rate
- Antepartum uterine haemorrhage requiring immediate delivery
- Eclampsia and severe pre-eclampsia requiring delivery
- Intrauterine fetal death
- Suspected intrauterine infection
- Placenta praevia
- Abruptio placenta
- Any other conditions of the mother or fetus, in which continuation of pregnancyis hazardous
- Known hypersensitivity to the active substance or any of the excipients

■ SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When atosiban is used in patients in whom premature rupture of membranes cannot be excluded, the benefits of delaying delivery should be balanced against the potential risk of chorioamnionitis.

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys (see sections POSOLOGY AND METHOD OF ADMINISTRATION and PHARMACOKINETIC PROPERTIES).

Atosiban has not been used in patients with an abnormal placental site.

There is only limited clinical experience in the use of atosiban in multiple pregnancies or the gestational age group between 24 and 27 weeks because of the small number of patients treated. The benefit of TRACTOCILE® in these subgroups is therefore uncertain.

Re-treatment with TRACTOCILE® is possible, but there is only limited clinical experience available with multiple re-treatments, up to 3 re-treatments (see section POSOLOGY AND METHOD OF ADMINISTRATION).

In case of intrauterine growth retardation, the decision to continue or reinitiate the administration of TRACTOCILE® depends on the assessment of fetal maturity. Monitoring of uterine contractions and fetal heart rate during administration of atosiban and in case of persistent uterine contractions should be considered.

As an antagonist of oxytocin, atosiban may theoretically facilitate uterine relaxation and post-partum bleeding, therefore blood loss after delivery should be monitored. However, inadequate uterus contraction post-partum was not observed during the clinical trials.

Multiple pregnancy and tocolytics like calcium channel blockers and betamimetics are known to be associated with increased risk of pulmonary oedema. Therefore atosiban should be used with caution in case of multiple gestations and/or concomitant administration of other tocolytics.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

It is unlikely that atosiban is involved in cytochrome P450 mediated drug-drug interactions, as in vitro investigations have shown that atosiban is not a substrate for the cytochrome P450 system and does not inhibit the drug metabolising cytochrome P450 enzymes.

Interaction studies were performed in healthy, female volunteers with betamethasone and labetalol. No clinically relevant interaction was observed between atosiban and betamethasone. When atosiban and labetalol were co-administered, C_{max} of labetalol was decreased by 36% and T_{max} increased by 45 minutes. However, the extent of labetalol bioavailability in terms of AUC did not change. The interaction observed has no clinical relevance. Labetalol had no effect on atosiban pharmacokinetics.

No interaction study has been performed with antibiotics, ergot alkaloids, and anti-hypertensive agents other than labetalol.

PREGNANCY AND LACTATION

Atosiban should only be used when preterm labour has been diagnosed between 24 and 33 completed weeks of gestation.

In atosiban clinical trials no effects were observed on lactation. Small amounts of atosiban have been shown to pass from plasma into the breast milk of lactating women.

Embryo-fetal toxicity studies have not shown toxic effects of atosiban. No studies were performed that covered fertility and early embryonic development (see section PRECLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable.

UNDESIRABLE EFFECTS

Possible undesirable effects of atosiban were described for the mother during the use of atosiban in clinical trials. The observed undesirable effects were generally of a mild severity. In total 48% of the patients treated with atosiban experienced undesirable effects.

For the newborn, the clinical trials did not reveal any specific undesirable effects of atosiban. The infant adverse events were in the range of normal variation and were comparable with both placebo and beta-mimetic group incidences.

The undesirable effects in the women were the following:

MedDRA Organ Class	Verycommon (≥10%)	Common (≥1-<10%)	Uncommon (≥0.1-<1%)	Rare (≥0.01-<0.1%)
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		Hyperglycaemia		
Psychiatric disorders			Insomnia	
Nervous system disorders		Headache, dizziness		
Cardiac disorders		Tachycardia		
Vascular disorders		Hypotension		
Gastrointestinal disorders	Nausea	Vomiting		
Skin and subcutaneous tissue disorders			Pruritus, rash	
Reproductive system and breast disorders				Uterine haemorrhage, uterine atony
General disorders and administration site conditions		Hot flushes, injection site reaction	Fever	

Respiratory events like dyspnoea and pulmonary oedema, particularly in association with concomitant administration of other tocolytics like calcium antagonists and beta-mimetics and/or multiple pregnancy, have been reported during the post-marketing.

■ OVERDOSE

Few cases of atosiban overdosing were reported. They occurred without any specific signs or symptoms. There is no known specific treatment in case of an overdose.

■ PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other gynecologicals, ATC code: G02CX01

TRACTOCILE® contains atosiban (INN), a synthetic peptide ([Mpa^1,D-Tyr(Et)^2,Thr^4,Orn^8]-oxytocin) which is a competitive antagonist of human oxytocin at receptor level. In rats and guinea pigs, atosiban was shown to bind to oxytocin receptors,to decrease the frequency of contractions and the tone of the uterine musculature,resulting in a suppression of uterine contractions. Atosiban was also shown to bind to the vasopressin receptor, thus inhibiting the effect of vasopressin. In animals atosiban did not exhibit cardiovascular effects.

In human preterm labour, atosiban at the recommended dosage antagonises uterine contractions and induces uterine quiescence. The onset of uterine relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence (≤ 4 contractions/hour) for 12 hours.

Phase III clinical trials (CAP-001 studies) included data from 742 women who werediagnosed with preterm labour at 23-33 weeks of gestation and were randomised to receive either atosiban (according to this labelling) or ß-agonist (dose-titrated).

Primary endpoint: the primary efficacy outcome was the proportion of women remaining undelivered and not requiring alternative tocolysis within 7 days of treatment initiation. The data show that 59.6% (n=201) and 47.7% (n=163) of atosiban- and ß-agonist-treated women (p=0.0004), respectively, were undelivered and did not require alternative tocolysis within 7 days of starting treatment. Most of the treatment failures in CAP-001 were caused by poor tolerability. Treatment failures caused by insufficient efficacy were significantly (p=0.0003) more frequent in atosiban (n=48, 14.2%) than in the ß-agonisttreated women (n=20, 5.8%).

In the CAP-001 studies the probability of remaining undelivered and not requiring alternative tocolysis within 7 days of treatment initiation was similar for atosiban and beta-mimetics treated women at gestational age of 24-28 weeks. However, this finding is based on a very small sample (n=129 patients).

Secondary endpoints: secondary efficacy parameters included the proportion of women remaining undelivered within 48 h of treatment initiation. There was no difference between the atosiban and beta-mimetic groups with regard to this parameter.

Mean (SD) gestational age at delivery was the same in the two groups: 35.6 (3.9) and 35.3 (4.2) weeks for the atosiban and ß-agonist groups respectively (p=0.37). Admission to a neonatal intensive care unit (NICU) was similar for both treatment groups (approximately 30%), as was length of stay and ventilation therapy. Mean (SD) birth weight was 2491 (813) g in the atosiban group and 2461 (831) g in the ß-agonist group (p=0.58).

Fetal and maternal outcome did apparently not differ between the atosiban and the ß-agonist group, but the clinical studies were not powered enough to rule out a possible difference.

Of the 361 women who received atosiban treatment in the phase III studies, 73 received at least one re-treatment, 8 received at least 2 re-treatments and 2 received 3 re-treatments (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

As the safety and efficacy of atosiban in women with a gestational age of less than 24 completed weeks has not been established in controlled randomised studies, the treatment of this patient group with atosiban is not recommended (see section CONTRAINDICATIONS).

In a placebo-controlled study, fetal/infant deaths were 5/295 (1.7%) in the placebo group and 15/288 (5.2%) in the atosiban group, of which two occurred at five and eight months of age. Eleven out of the 15 deaths in the atosiban group occurred in pregnancies exposed to atosiban at a gestational age of 20 to 24 weeks, although in this subgroup patient distribution was unequal (19 women on atosiban, 4 on placebo). For women exposed at a gestational age greater than 24 weeks there was no difference in mortality rate (1.7% in the placebo group and 1.5% in the atosiban group).

■ PHARMACOKINETIC PROPERTIES

In healthy non-pregnant subjects receiving atosiban infusions (10 to 300 µg/min over 12 hours), the steady state plasma concentrations increased proportionally to the dose.

The clearance, volume of distribution and half-life were found to be independent of the dose.

In women in preterm labour receiving atosiban by infusion (300 µg/min for 6 to 12 hours), steady state plasma concentrations were reached within one hour following the start of the infusion (mean 442 ± 73 ng/ml, range 298 to 533 ng/ml).

Following completion of the infusion, plasma concentration rapidly declined with an initial (tα) and terminal (tß) half-life of 0.21 ± 0.01 and 1.7 ± 0.3 hours, respectively. Mean value for clearance was 41.8 ± 8.2 1/h. Mean value of volume of distribution was 18.3 ± 6.8 l.

Plasma protein binding of atosiban is 46 to 48% in pregnant women. It is not known whether the free fraction in the maternal and fetal compartments differ substantially. Atosiban does not partition into red blood cells.

Atosiban passes the placenta. Following an infusion of 300 µg/min in healthy pregnant women at term, the fetal/maternal atosiban concentration ratio was 0.12.

Two metabolites were identified in the plasma and urine from human subjects. The ratios of the main metabolite M1 (des-(Orn^8, Gly-NH$_2^9$)-[Mpa^1, D-Tyre(Et)^2, Thr^4]-oxytocin) to atosiban concentrations in plasma were 1.4 and 2.8 at the second hour and at the end of the infusion respectively. It is not known whether M1 accumulates in tissues. Atosiban is found in only small quantities in urine, its urinary concentration is about 50 times lower than that of M1. The proportion of atosiban eliminated in faeces is not known. The main metabolite M1 is approximately 10 times less potent than atosiban in inhibiting oxytocin-induced uterine contractions in vitro. Metabolite M1 is excreted in milk (see section PREGNANCY AND LACTATION).

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys (see section POSOLOGY AND METHOD OF ADMINISTRATION and SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

It is unlikely that atosiban inhibits hepatic cytochrome P450 isoforms in humans (see section INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

PRECLINICAL SAFETY DATA

No systemic toxic effects were observed during the two-week intravenous toxicity studies (in rats and dogs) at doses which are approximately 10 times higher than the human therapeutic dose, and during the three-months toxicity studies in rats and dogs (up to 20 mg/kg/day s.c.). The highest atosiban subcutaneous dose not producing any adverse effects was approximately two times the therapeutic human dose.

No studies were performed that covered fertility and early embryonic development. Reproduction toxicity studies, with dosing from implantation up to late stage pregnancy, showed no effects on mothers and fetuses. The exposure of the rat fetus was approximately four times that received by the human fetus during intravenous infusions in women. Animal studies have shown inhibition of lactation as expected from the inhibition of action of oxytocin.

Atosiban was neither oncogenic nor mutagenic in in vitro and in vivo tests.

INCOMPATIBILITIES

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

■ SHELFLIFE

■ 4 years

Solution for injection

Once the vial has been opened, the product must be used immediately.

Concentrate for solution for infusion

Once the vial has been opened, the dilution must be performed immediately.

Diluted solution for intravenous administration should be used within 24 hours after preparation.

■ SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C – 8°C. Store in the original container.

■ PACK SIZES

Solution for injection

One vial of solution for injection contains 0.9 ml.

Concentrate for solution for infusion

One vial of concentrate for solution for infusion contains 5 ml.

INSTRUCTIONS FOR USE AND HANDLING

Solution for injection

The vials should be inspected visually for particulate matter and discoloration prior to administration.

Preparation of the initial intravenous injection

Withdraw 0.9 ml of a 0.9 ml labelled vial of TRACTOCILE® 7.5 mg/ml, solution for injection and administer slowly as an intravenous bolus dose over one minute, under adequate medical supervision in an obstetric unit. The TRACTOCILE® 7.5 mg/ml, solution for injection should be used immediately.

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products (see section INCOMPATIBILITIES).

Concentrate for solution for infusion

The vials should be inspected visually for particulate matter and discoloration prior to administration.

Preparation of the intravenous infusion solution:

For intravenous infusion, following the bolus dose, TRACTOCILE® 7.5 mg/ml, concentrate for solution for infusion should be diluted in one of the following solutions:

- 0.9% w/v NaCl
- Ringer's lactate solution
- 5% w/v glucose solution

Withdraw 10 ml solution from a 100 ml infusion bag and discard. Replace it by 10 ml TRACTOCILE® 7.5 mg/ml concentrate for solution for infusion from two 5 ml vials to obtain a concentration of 75 mg atosiban in 100 ml. The loading infusion is given by infusing 24 ml/hour (i.e. 18 mg/h) of the above prepared solution over the 3 hour period under adequate medical supervision in an obstetric unit. After three hours the infusion rate is reduced to 8 ml/hour.

Prepare new 100 ml bags in the same way as described to allow the infusion to be continued.

If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation.

To achieve accurate dosing, a controlled infusion device is recommended to adjust the rate of flow in drops/min. An intravenous microdrip chamber can provide a convenient range of infusion rates within the recommended dose levels for TRACTOCILE®.

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products. If other medicinal products need to be given intravenously at the same time, the intravenous cannula can be shared or another site of intravenous administration can be used. This permits the continued independent control of the rate of the infusion.

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