

“隆柏”福祿安持續性注射液

Fluanxol Depot 1ml

衛署藥輸字第005037號

本藥限由醫師使用

“隆柏”福祿安長效注射液100公絲/公撮

Fluanxol Depot Injection 100mg/ml

衛署藥輸字第012803號

本藥限由醫師使用

1. 主成份

Fluanxol Depot 1ml：每ml含Cis(Z)-flupentixol decanoate 20mg

Fluanxol Depot Injection 100mg/ml：每ml含Cis(Z)-flupentixol decanoate 100mg

2. 賦形劑

Triglycerides, medium chain (Ph. Eur.)

3. 藥品形狀

注射用溶液

20 毫克/毫升：透明，無色到淺黃色的油質溶液，沒有懸浮微粒。

100 毫克/毫升：透明，略黃到黃色的油質溶液，沒有懸浮微粒。

4. 臨床資訊：

4.1 適應症

精神病狀態

4.2 用法用量

成人

為達到最大精神病症狀治療效果及最少的副作用，每次注射的劑量和間隔時間應視病人個別之情況而作調整。

Flupentixol decanoate 20 毫克/毫升

維持劑量通常是依據治療反應，間隔二～四星期注射20-40 毫克(1-2 毫升)。

有些病人可能需要調高劑量或縮短注射的投與間隔。Flupentixol decanoate 20 毫克/毫升

不適合作為鎮靜劑使用。若注射量大於2 毫升應分兩劑於兩個部位注射。

如果20 毫克/毫升溶液需要的使用量超過2-3 毫升，建議使用高濃度的flupentixol decanoate 100 毫克/毫升。

病情加重惡化或急性復發，可能需要每隔兩星期(或者某些特別的情況在短期間內須每星期)單一注射400毫克。

Flupentixol decanoate 100 毫克/毫升

劑量範圍在每隔四週注射50 毫克(0.5 毫升) 到每隔兩週注射 200 毫克(2毫升)。但有些病人可能需要每週注射 400 毫克(4 毫升)。注射量若大於2 毫升應分兩劑於兩個部位注射。

用高濃度注射液來治療嚴重的精神病，通常在四～六個月可達到病情控制效果，隨即應逐漸降低劑量持續治療。

從flupentixol 口服錠劑改為flupentixol decanoate治療，應遵循下列換算方式：

每天口服flupentixol的毫克量 $\times 4$ = 每隔二週flupentixol decanoate肌肉注射毫克量

每天口服flupentixol的毫克量 $\times 8$ = 每隔四週flupentixol decanoate肌肉注射毫克量

在第一次接受注射後，flupentixol 口服治療仍應繼續服用，但應減少劑量。

其他depot製劑換算flupentixol decanoate的效價比例：40毫克flupentixol decanoate 相當於 25 毫克fluphenazine decanoate。

flupentixol decanoate的後續劑量和每次注射間隔應依病人療效反應作調整。

老年人

老年患者應投與建議劑量使用範圍之最低量。

腎臟功能受損者

腎功能受損者，可以一般劑量投與flupentixol decanoate。

肝功能受損者

須小心投與，如有必要，建議檢測血清值。

孩童

因缺乏臨床經驗，不建議使用。

用法

Flupentixol decanoate 肌肉注射，在臀部上外部四分之一區域。注射量若大於2毫升應分兩劑於兩個部位注射。局部耐受性佳。

4.3 禁忌症

對flupentixol或其賦形劑會有過敏反應之病人。

循環性虛脫、任何原因(如酒精、巴比妥酸鹽或鴉片劑中毒)導致之中樞神經系統抑制、昏迷、惡血質、嗜絡細胞瘤等。



94.12.28

4.4 特別警語及注意事項

警語
任何抗精神病藥物都可能引起抗精神病藥急性症候群(體溫過高、肌肉僵硬、意識模糊、自主神經不安定)。效價較強的劑劑可能產生之危險更大。在致死案例中，病人存在有器質性腦病變、弱智、鴉片、酒精濫用等，症狀會更加過度顯現。

如遇上述情形應即停止使用抗精神病藥物。使用症狀治療及一般支持療法。Dantrolene 和 bromocriptine 可能有幫助。
停用口服抗精神病藥物，症狀可能持續一週以上，當投與持續性劑型時，則會持續更久。

注意事項
如同其他抗精神病藥物，flupentixol decanoate應小心的使用於患有器質性腦病變、痙攣和進行性肝病的病人。即使是低劑量的flupentixol decanoate不建議投與過度激動或過度活躍的病人，它的激活作用會導致這些症狀惡化。
如同其他的抗精神病藥物，flupentixol decanoate可能改變胰島素和葡萄糖之反應，因此糖尿病患者使用降血糖藥物須被調整。
病人長期治療，尤其是使用高劑量投與時，應小心監測，並定期評估以決定是否降低維持劑量。

4.5 與其他藥物之交交互作用及其他形式之交交互作用

併用時應注意事項
Flupentixol decanoate 可能會增強酒精的鎮靜效果、巴比妥酸鹽和其他中樞神經抑制劑的作用。
抗精神病藥物可能增加或減少抗高血壓藥物的效果；guanethidine及其作用相似化合物之抗高血壓療效會減弱。
抗精神病藥物和鋰鹽併用會增加神經毒性的危險。
三環抗抑鬱劑和抗精神病藥物會相互抑制其代謝作用。
Flupentixol decanoate 可能會減低levodopa 和腎上腺素性藥物的療效。與metoclopramide 及 piperazine併用時會增加產生錐體外症候群之危險。

4.6 懷孕及授乳

懷孕
孕婦不應投與Fluanxol Depot，除非對病人所預期益處高於對胎兒理論上風險。產婦在懷孕末期或分娩時投與抗精神病藥物，新生兒可能產生中毒的症狀，如嗜睡症、震顫和過度興奮及apgar評分也會偏低。
從動物生殖試驗中並未證實會增加胚胎損害之發生率或對生殖過程中其他對身心有害的作用。

授乳
當投與治療劑量時，在乳汁中僅驗出微量的殘留，其不會影響嬰兒。嬰兒攝入的劑量低於母親每日劑量之0.5% (以毫克/kg估算)。若考慮臨床的重要性，以flupentixol decanoate治療期間可以持續哺乳，但建議對嬰兒多加注意，尤其是在出生之後的前四週。

4.7 影響駕駛和機械操作能力

flupentixol decanoate投與中-低劑量範圍時非鎮靜藥物(最多100mg/第二週)。然而當病人投與抗精神病藥物時可能被預期它對一般的注意力和專注力會有些減弱，因此駕駛和機械操作的能力應該加以注意。

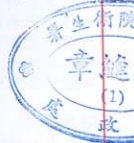
4.8 副作用

副作用的頻度和強度較常出現在治療的前期階段，並在持續治療後，會逐漸減弱。
特別是在投予藥物後的前幾天及治療早期，可能會產生行動異常。大部份的副作用可藉由降低劑量及/或抗巴金森藥物而得到滿意的控制效果。不建議以抗巴金森藥物做為例行性之預防使用。抗巴金森藥物不會減輕運動困難的情況甚至可能惡化，建議減少劑量，若可能的話則停止治療。持續的靜坐不能，投予benzodiazepine或 propranolol可能有幫助。可能引起失眠或不安，特別是病人原本服用鎮定效果之抗精神病劑。

臨床試驗

MedDRA分級/較恰當的用語：
非常常見 (> 1/10); 常見 (> 1/100, < 1/10); 不常見 (> 1/1,000, < 1/100);
罕見 (> 1/10,000, < 1/1,000); 非常罕見 (< 1/10,000)。

MedDRA分級	頻率	較恰當的用語
代謝和營養異常	不常見 (> 1/1,000, < 1/100)	體重增加
精神異常	常見 (> 1/100, < 1/10)	沮喪、失眠、激躁
	不常見 (> 1/1,000, < 1/100)	攻擊性反應
神經系統異常	非常常見 (> 1/10)	錐體外症候群、巴金森氏症、震顫、靜坐不能
	常見 (> 1/100, < 1/10)	肌張力不全、運動困難、語言障礙
	不常見 (> 1/1,000, < 1/100)	頭暈
視覺異常	常見 (> 1/100, < 1/10)	眼動轉變
	不常見 (> 1/1,000, < 1/100)	調節異常
一般心血管系統異常	常見 (> 1/100, < 1/10)	低血壓
腸胃系統異常	常見 (> 1/100, < 1/10)	唾液增加、吞嚥困難
	不常見 (> 1/1,000, < 1/100)	便秘
全身性異常	常見 (> 1/100, < 1/10)	疲勞、虛弱
診察	不常見 (> 1/1,000, < 1/100)	體重增加



下列發生頻率曾在臨床試驗中被報告過 (N=702 病患):

皮膚及附屬組織異常 不常見-皮膚炎

中樞和周邊神經系統異常 非常常見-錐體外症候群可能出現，尤其是在治療的前期。

大部分患者其副作用通常經由劑量的降低或抗巴金森氏症藥物的使用而有良好的控制。不建議將抗巴金森氏症藥物作為常規的預防使用。

抗巴金森氏症藥物並不能減輕遲發性運動不能，甚至還會使其加重。建議降低劑量或必要時停止治療。

對於持續性靜坐不能Benzodiazepine或 propranolol，可能有效。

下列錐體外症候群曾被報導過：巴金森氏症、震顫、痙攣 (= 靜坐不能)、肌張力不全 (僵直)、急性運動困難、眼動轉變。

常見-語言障礙 不常見-頭暈

自主神經系統異常 常見-唾液增加

視覺異常 不常見-調節異常

腸胃系統異常 常見-吞嚥困難 不常見-便秘

一般心血管系統異常 常見-低血壓

全身性異常 常見-疲勞、虛弱

上市後報告

抗精神病藥惡性症候群曾被報導過，一些長期接受治療的病人偶爾可能會出現遲發性運動不能。抗巴金森氏症藥物並不能減輕這些症狀，甚至可能使其惡化。建議必要時降低劑量或停止治療。有很少的報告指出肝功能測試會有短暫輕微變化。

4.9 過量

依照給藥劑量規定，不可能導致過量發生。

症狀：嗜睡、昏迷、錐體外症候群、痙攣、休克、體溫過高或過低。

治療：採症狀及支持療法。維持呼吸和心血管系統的正常措施應該立即建立。腎上腺素不應使用，會使血壓過低。可用diazepam治療痙攣，而錐體外症候群可用biperiden治療。

5. 藥理性質

藥效性質(Pharmacodynamic)

藥理療效分類：抗精神病藥物 - thioxanthene衍生物。

ATC-code: N 05 AF 01

作用機轉

Cis(Z)-flupentixol是thioxanthene類的抗精神病藥物。

抗精神病藥物的抗精神病作用與阻斷dopamine接受器有關，但也可能是阻斷5-HT (5-hydroxytryptamine) 接受器所造成。cis(Z)-flupentixol在體外及體內對dopamine D1 及 D2 接受器皆具有高度親和力，但 fluphenazine在體內幾乎只選擇 D2。非典型的抗精神病藥物clozapine如同cis(Z)-flupentixol，不論在體外及體內，對 D1和D2接受器都具有親和力。Cis(Z)-flupentixol對 α 1-腎上腺接受器和5-HT2接受器都有高度親和力，雖然低於chlorprothixene、高劑量的phenothiazines 和 clozapine，但對cholinergic muscarine接受器則不具親和力。故僅有輕微的抗組織胺性質且具阻斷 α 2-腎上腺接受器的活性。

針對抗精神病藥物活性 (阻斷dopamine接受器) 的所有行為試驗中，cis(z)-flupentixol已被證實為有效的抗精神病藥物。在體內試驗模式及體外試驗中發現平均每日口服抗精神病藥物之劑量與dopamine結合位置的親和力有關。

老鼠口周圍活動與 D1接受器被刺激或D2接受器被阻斷的數目而定。cis(Z)-flupentixol有阻止這些活動的效果。同樣地，在猴子的研究結果顯示，口部運動過度與D1接受器的被刺激較有關連。對D2接受器的超敏感度則較低。因此得到的結論是在人類活化D1接受器也會造成類似的反應，如運動不能 (dyskinesia)。因此，阻斷D1接受器應該是有利作法。

如同其他的抗精神病藥物，flupentixol會增加血清泌乳激素的量。

藥理研究顯示，cis(Z)-flupentixol decanoate油溶基劑具有長效的抗精神病作用，持續一段長期治療，為要達到一定效果，使用depot比每天口服flupentixol使用的藥量為低。巴比妥酸鹽引起的中到短程嗜睡現象，在老鼠試驗中證明僅在高劑量的情況下才會發生。因此，接受depot劑型的病人不會干擾及影響麻醉效果。

臨床效果

临床上，flupentixol decanoate通常是用於慢性精神病患的維持療法。直到劑量增加，抗精神疾病的效果也會增加。當flupentixol decanoate劑量從低劑量到中度劑量(100 毫克/2 週) 不具有鎮靜效果，要達到非特殊性鎮靜效果須投與較高的劑量。(病情加重或急性復發，可採間隔兩週注射，每次400 毫克 (或有特別需要時，在短期內可採每週注射一次) (採用高濃度的注射液)。

Flupentixol decanoate 對於治療冷漠、退縮、抑鬱和缺乏動機的病人特別有效。

Flupentixol decanoate 可以長期使用，特別是針對未能確實服藥的病人。對口服藥物遵醫囑性不佳的病人，

Flupentixol decanoate可以預防復發的頻率。

5.2 藥動性質(Pharmacokinetic properties)

吸收

cis(Z)-flupentixol 和decanoic acid經酯化，轉化cis(Z)-flupentixol為親脂性物質- cis(Z)-flupentixol decanoate。溶於油，經肌肉注射，酯緩慢滲透進體內，隨即迅速水解，游離出活性cis(Z)-flupentixol。

最高血清濃度於肌肉注射後3-7天會達到，連續投與三個月，會達到半衰期為3星期 (依照depot的釋出而定) 之穩定狀態。

分佈

擬似分布體積 (Vd) β 約為 14.1 L/kg。血漿蛋白結合率約 99 %。

生物轉換

cis(Z)-flupentixol 的代謝有三個主要途徑—sulphoxidation 側鏈、N-dealkylation 及 glucuronic acid 結合。代謝產物不具有抗精神病之藥理的活性。Cis(Z)-flupentixol 在腦部或其他組織中優於其代謝產物。

排除

cis(Z)-flupentixol 的排除半衰期 ($t_{1/2\beta}$) 約為 35 小時，平均全身性清除率 (Cl_s) 約為 0.29 L/min。

Cis(Z)-flupentixol 主要經由糞便排泄，也有少數經由尿液排出。在男性投與使用氚 (tritium) 標記 flupentixol 時，顯示出經由糞便排泄的量約經由尿液排除量的四倍。

在哺乳婦女中僅有少量 cis(Z)-flupentixol 排至乳汁中。Flupentixol 在乳汁中濃度與血清濃度的比值平均約為 1.3。

線性
動力學性質為線性的。cis(Z)-flupentixol 平均穩定血清濃度為 6nmol/L 相當於每隔兩週注射 40 毫克劑量 cis(Z)-flupentixol decanoate。

老年患者

並未對老年患者進行藥物動力學研究。然而對於相關的 thioxanthene 類藥物如 zuclopenthixol 進行的研究，其藥物動力學數據和病人年紀無關。

腎功能受損者

基於上述排除的特性，認為在腎功能受損者其血清中濃度並不太會受影響。

肝功能受損者

並無相關的資料。

藥物動力學/藥效動力學相關性 (Pharmacokinetic / Pharmacodynamic)

藥物血中濃度保持為 1-3ng/ml (2-8 nmol/L) 及血中藥物最大/最小濃度浮動範圍 <2.5，建議作為治療患有輕度-中度精神分裂症之病人的維持治療準則。

在藥物動力學，40 毫克/2週的 cis(Z)-flupentixol decanoate 劑量相當於每日口服 10 毫克 flupentixol 的劑量。

5.3 臨床前安全訊息

急性毒性

Flupentixol 具有低的急性毒性。

慢性毒性

慢性毒性的研究並未發現使用 flupentixol 會有慢性毒性。

生殖毒性

在生育年齡的婦女使用 flupentixol 或 cis(Z)-flupentixol decanoate 的生殖毒性研究並未有特別的影響。

致癌性

Flupentixol 並無致癌性質。

局部毒性

局部耐受力良好。注射水溶液的神經疾病藥物有發生過局部肌肉受傷。經由對兔子進行脂溶性 cis(Z)-flupentixol decanoate 的肌肉注射，只會產生輕微出血和水腫。

6. 產品資訊

6.1 賦形劑

Triglycerides, medium chain (Ph. Eur.)

6.2 配伍禁忌

Flupentixol decanoate 不能用芝麻油作油質基劑作為 depot 製劑，因為這些配方混合會因藥物動力學特質而產生變化。

6.3 貯架期

20 毫克/毫升 Ampoules 至多五年，15°C 以下，避光貯存。

100 毫克/毫升 Ampoules 至多五年，15°C 以下，避光貯存。

包裝上均標示有限期限。

6.4 儲存

儲存溫度 15°C 以下，容器需有外包裝（避免光線照射）。

6.5 包裝

每盒 100 支以下安瓿裝

6.6 使用/處理說明

無。

【修訂日期】

2005 年 4 月

製造廠：H. Lundeck A/S

廠址：Ottiliavej 9 DK-2500 Copenhagen-Valby, Denmark

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Fluanxol® Depot

20 mg/ml - 100 mg/ml solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Fluanxol® Depot 20 mg/ml solution for injection
Fluanxol® Depot 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cis(Z)-flupentixol decanoate 20 mg/ml.
Cis(Z)-flupentixol decanoate 100 mg/ml.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

20 mg/ml: Clear, colourless to slightly yellowish oil, practically free from particles.
100 mg/ml: Clear, yellowish to yellow oil, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maintenance treatment of schizophrenia and other psychoses, especially with symptoms such as hallucinations, delusions and thought disturbances along with apathy, anergy, depression and withdrawal.

4.2 Posology and method of administration

Adults

Dosage and interval between injections should be adjusted for each individual patient so as to achieve a maximum suppression of psychotic symptoms with a minimum of side effects.

Flupentixol decanoate 20 mg/ml
In the maintenance treatment the dosage range would normally be 20-40 mg (1-2 ml) at intervals of 2 to 4 weeks depending on the response. Some patients may need larger doses or need them at shorter intervals. Flupentixol decanoate 20 mg/ml is unsuitable for patients in whom sedation is required. Injection volumes larger than 2 ml should be distributed between two injection sites.

If volumes larger than 2-3 ml of the 20 mg/ml solution are required the more concentrated solutions (flupentixol decanoate 100 mg/ml) should be preferred.

During an exacerbation or acute relapse of the illness single injections of as much as 400 mg fortnightly (or in the occasional cases weekly for a short period) may be required.

Flupentixol decanoate 100 mg/ml
Dosage range lies between 50 mg (0.5 ml) every 4 weeks to 300 mg (3 ml) every 2 weeks but some patients may require up to 400 mg (4 ml) weekly. Injection volumes larger than 2 ml should be distributed between two injection sites.

Adequate control of severe psychotic symptoms by the concentrated injection fluids is usually achieved within 4 to 6 months and may justify gradual return to lower dose maintenance.

When changing the medication from oral flupentixol to maintenance treatment with flupentixol decanoate the following guidelines should be used:

x mg p.o. daily corresponds to 4x mg decanoate every 2 weeks.
x mg p.o. daily corresponds to 8x mg decanoate every 4 weeks.

Oral flupentixol should be continued during the first week after the first injection but in diminishing dosage.

Patients being transferred from other depot preparations should receive a dose in the ratio of 40 mg flupentixol decanoate equivalent to 25 mg fluphenazine decanoate.

Subsequent doses of flupentixol decanoate and interval between injections should be adjusted to the patient's response.

Elderly patients
Elderly patients should receive dosages in the lower end of the dosage range.

Reduced renal function
Flupentixol decanoate can be given in usual doses to patients with reduced renal function.

Reduced liver function
Careful dosing and, if possible, a serum level determination is advisable.

Children
Not recommended due to lack of clinical experience.

Method of administration
Flupentixol decanoate is administered by intramuscular injection into the upper outer quadrant of the gluteal region. Injection volumes exceeding 2 ml should be distributed between two injection sites. Local tolerability is good.

4.3 Contra-indications

Hypersensitivity to flupentixol or any of the excipients.

Circulatory collapse, central nervous system depression due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), comatose states, blood dyscrasias, phaeochromocytoma.

4.4 Special warnings and special precautions for use

Warnings
The possibility of development of neuroleptic malignant syndrome (hyperthermia, rigidity, fluctuating consciousness, instability of the autonomous nervous system) exists with any neuroleptic. The risk is possibly greater with the more potent agents. Patients with pre-existing organic brain syndrome, mental retardation, opiate and alcohol abuse are overrepresented among fatal cases.

Treatment: Discontinuation of the neuroleptic. Symptomatic treatment and use of general supportive measures.
Dantrolene and bromocriptine may be helpful.
Symptoms may persist for more than a week after oral neuroleptics are discontinued and somewhat longer when associated with the depot forms of the drugs.

Precautions
Like other neuroleptics flupentixol decanoate should be used with caution in patients with organic brain syndrome, convulsive disorders and advanced hepatic disease.

In the lower dosage range flupentixol decanoate is not recommended for excitable or overactive patients since its activating effect may lead to exaggeration of these characteristics.

As described for other psychotropics flupentixol decanoate may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

Patients on long-term therapy, particularly on high doses, should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

4.5 Interaction with other medicaments and other forms of interaction

Combinations requiring precautions for use
Flupentixol decanoate may enhance the sedative effect of alcohol and the effects of barbiturates and other CNS depressants.
Neuroleptics may increase or reduce the effect of antihypertensive drugs; the antihypertensive effect of guanethidine and similar acting compounds is reduced.
Concomitant use of neuroleptics and lithium increases the risk of neurotoxicity.
Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other.
Flupentixol decanoate may reduce the effect of levodopa and the effect of adrenergic drugs.
Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal symptoms.

4.6 Pregnancy and lactation

Pregnancy
Fluanxol Depot should not be administered during pregnancy unless the expected benefit to the patient outweighs the theoretical risk to the foetus. The newborns of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyperexcitability and have a low apgar score.

Animal-reproduction studies on flupentixol have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproduction process.

Lactation
As flupentixol is found in breast milk in low concentrations it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is less than 0.5% of the weight related maternal dose (in mg/kg). Breast-feeding can be continued during flupentixol decanoate therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after giving birth.

4.7 Effects on ability to drive and use machines

Flupentixol decanoate is a non-sedating drug in the low-moderate dosage range (up to 100 mg/2nd week).
However, patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

4.8 Undesirable effects

Unwanted effects are for the majority dose dependent. The frequency and severity of unwanted effects are most pronounced in the early phase of treatment and decline during continued treatment.

Movement disorders may occur, especially during the first few days after an injection and in the early phase of treatment.
In most cases these side effects can be satisfactorily controlled by reduction of dosage and/or antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended.
Antiparkinsonian drugs do not alleviate tardive dyskinesias and may aggravate them. Reduction in dosage or, if possible, discontinuation of therapy is recommended.
In persistent akathisia a benzodiazepine or propranolol may be useful.
Insomnia (transient) and unrest occur especially, if patients are switched over from neuroleptics with sedative effect.

Clinical trials

In the listing below the following convention is used:
MedDRA system organ class / preferred term
Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000).

MedDRA SOC	Frequency	Preferred Term
Metabolism and nutrition disorders	Uncommon (>1/1,000, < 1/100)	Decreased appetite
Psychiatric disorders	Common (>1/100, < 1/10)	Depression, Insomnia, agitation.
	Uncommon (>1/1,000, < 1/100)	Aggression
Nervous system disorders	Very common (>1/10)	Extrapyramidal disorder, parkinsonism, tremor, akathisia.
	Common (>1/100, < 1/10)	Dystonia, dyskinesia, Speech disorder
	Uncommon (>1/1,000, < 1/100)	Dizziness
Eye disorders	Common (>1/100, < 1/10)	Oculogyration
	Uncommon (>1/1,000, < 1/100)	Accommodation disorder
Vascular disorders	Common (>1/100, < 1/10)	Hypotension
Gastrointestinal disorders	Common (>1/100, < 1/10)	Salivary hypersecretion, dysphagia
	Uncommon (>1/1,000, < 1/100)	Constipation
General disorders and administration site conditions	Common (>1/100, < 1/10)	Fatigue, asthenia
Investigations	Uncommon (>1/1,000, < 1/100)	Weight increased

Post marketing reports

Neuroleptic malignant syndrome has been reported.

Tardive dyskinesia may occur occasionally in some patients on long-term therapy. Antiparkinsonian drugs do not alleviate these symptoms and may aggravate them. Reduction in dosage or, if possible, discontinuation of therapy is recommended.

Transient slight alterations in liver function tests have infrequently been reported.

4.9 Overdose effects

Due to the administration form overdosage symptoms are unlikely to occur.

Symptoms: Somnolence, coma, movement disorders, convulsions, shock, hyper- or hypothermia.

Treatment: Treatment is symptomatic and supportive. Measures to support the respiratory and cardiovascular systems should be instituted. Epinephrine (adrenaline) should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal symptoms with biperiden.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Neuroleptics (antipsychotics)
ATC-code: N 05 AF 01

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Mechanism of action

Cis(Z)-flupentixol is a neuroleptic of the thioxanthene group. The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect but possibly also 5-HT (5-hydroxytryptamine) receptor blockade contributes. *In vitro* and *in vivo* cis(Z)-flupentixol has high affinity for both dopamine D₁ and D₂ receptors whereas fluphenazine is almost D₂ selective *in vivo*. The atypical antipsychotic, clozapine, shows - as cis(Z)-flupentixol – equiaffinity to D₁ and D₂ receptors both *in vitro* and *in vivo*.

Cis(Z)-flupentixol has high affinity for α₁-adrenoceptors and 5-HT₂ receptors, although lower than that of chlorprothixene, high-dose phenothiazines and clozapine, but no affinity for cholinergic muscarine receptors. It has only slight antihistaminergic properties and no α₂-adrenoceptor blocking activity.

Cis(Z)-flupentixol has proven to be a potent neuroleptic in all the behavioural studies for neuroleptic (dopamine receptor blocking) activity. Correlation is found in the *in vivo* test models, the affinity for dopamine D₂ binding sites *in vitro* and the average, daily oral antipsychotic doses.

Perioral movements in rats are dependent on D₁ receptor stimulation or blockade of the D₂ receptor population. The movements can be prevented by cis(Z)-flupentixol. Likewise, the results from investigations in monkeys indicate that oral hyperkinesia is more related to D₁ receptor stimulation and to a less degree to D₂ receptor supersensitivity. This leads to the suggestion that D₁ activation is responsible for similar effects in man, i.e. dyskinesia. Therefore, blockade of D₁ receptors should be advantageous.

Like most other neuroleptics, flupentixol increases the serum prolactin level.

Pharmacological studies have clearly demonstrated that cis(Z)-flupentixol decanoate in oil has a prolonged neuroleptic effect and that the amount of drug necessary to maintain a certain effect over a long period is considerably smaller with the depot preparation than with daily oral administration of flupentixol. A very modest and short-lasting potentiation of barbiturate-induced sleeping time in mice could be demonstrated only with high doses. It is unlikely, therefore, that any significant interference with anaesthetics would occur in patients receiving the depot preparation.

Clinical efficacy

In clinical use flupentixol decanoate is intended for the maintenance treatment of chronic psychotic patients. The antipsychotic effect increases with increasing dosages. In low to moderate dosages (up to 100 mg/2 weeks) flupentixol decanoate is nonsedating while some unspecific sedation may be expected when higher doses are administered.

Flupentixol decanoate is particularly useful in the treatment of apathetic, withdrawn, depressed and poorly motivated patients.

Flupentixol decanoate permits continuous treatment especially of those patients who are unreliable in taking the oral medication prescribed for them. Flupentixol decanoate thus prevents the frequent relapses due to noncompliance in patients on oral medication.

5.2 Pharmacokinetic properties

Absorption

By esterification of cis(Z)-flupentixol with decanoic acid cis(Z)-flupentixol has been converted to a highly lipophilic substance, cis(Z)-flupentixol decanoate. When dissolved in oil and injected intramuscularly the ester diffuses rather slowly from the oil to the body water phase where it is rapidly hydrolysed releasing the active cis(Z)-flupentixol.

Following intramuscular injection maximum serum concentration is generally reached over a period of 3-7 days. With an estimated half-life of 3 weeks (reflecting the release from the depot) steady state conditions will be attained after about 3 months’ repeated administration.

Distribution

The apparent volume of distribution (V_d)_β is about 14.1 l/kg. The plasma protein binding is about 99 %.

Biotransformation

The metabolism of cis(Z)-flupentixol proceeds along three main routes – sulfoxidation, side chain N-dealkylation and glucuronic acid conjugation. The metabolites are devoid of psychopharmacological activity. Cis(Z)-flupentixol dominates over metabolites in brain and other tissues.

Elimination

The elimination half-life (t_{1/2 β}) of cis(Z)-flupentixol is about 35 hours and the mean systemic clearance (Cl_s) is about 0.29 l/min. Cis(Z)-flupentixol is excreted mainly with feces, but also to some degree with the urine. When tritium labelled flupentixol was administered to man the excretion pattern shows the excretion via feces to be about 4 times the urinary excretion.

In nursing mothers cis(Z)-flupentixol is excreted in small amounts with the breast milk. The ratio milk conc./serum conc. in women is on an average 1.3.

Linearity

The kinetics is linear. The mean steady state pre-injection serum level of cis(Z)-flupentixol corresponding to a 40 mg dose of cis(Z)-flupentixol decanoate every 2 weeks is about 6 nmol/l.

Elderly patients

Pharmacokinetic investigations have not been done in elderly patients. However, for the related thioxanthene drug, zuclopenthixol, the pharmacokinetic parameters are widely independent of the age of the patients. *Reduced renal function*
Based on the above characteristics for elimination it is reasonable to assume that reduced kidney function is likely not to have much influence on the serum levels of parent drug.

Reduced hepatic function

No data available.

Pharmacokinetic / Pharmacodynamic relationship

A pre-injection serum (plasma) concentration of 1-3 ng/ml (2-8 nmol/l) and a max./min. fluctuation < 2.5 is suggested as a guideline for maintenance treatment of schizophrenic patients with a low-moderate degree of illness. Pharmacokinetically a dose of 40 mg/2 weeks of cis(Z)-flupentixol decanoate is equivalent to a daily oral dose of 10 mg flupentixol.

5.3 Preclinical safety data

Acute toxicity

Flupentixol has low acute toxicity.

Chronic toxicity

In chronic toxicity studies there were no findings of concern for the therapeutic use of flupentixol.

Reproduction toxicity

Based on data from reproduction toxicity studies there is no reason to have special concern for the use of flupentixol or cis(Z)-flupentixol decanoate in women of child-bearing potential.

Carcinogenicity

Flupentixol has no carcinogenic potential.

Local toxicity

The local tolerability is good. Local muscle damage is seen after injection of aqueous solutions of neuroleptics. After intramuscular injection in rabbits of cis(Z)-flupentixol decanoate in oil only slight haemorrhage and oedema was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Triglycerides, medium chain (Ph. Eur.)

6.2 Incompatibilities

Flupentixol decanoate should not be mixed with depot formulations with sesame oil as the vehicle because this would result in definite changes in the pharmacokinetic properties of the involved preparations.

6.3 Shelf life

20 mg/ml
Ampoules 5 years at max. 15°C, protected from light.

100 mg/ml
Ampoules 5 years at max. 15°C, protected from light.

Each pack has an expiry date.

6.4 Special precautions for storage

Store below 15°C.
Keep container in the outer carton (protected from light).

6.5 Nature and contents of container

20 mg/ml
Colourless glass (type I) ampoules of 1 ml and 2 ml.
Boxes of 1x1 ml and 10x1 ml, 1?2 ml and 10x2 ml.

100 mg/ml
Brown glass ampoules (type I) of 1 ml.
Boxes of 1x1 ml and 10x1 ml.

6.6 Instructions for use/handling

None.

7. MARKETING AUTHOTISATION HOLDER / MANUFACTURER

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