頗得斯安栓劑

Pentasa® Suppositories 1 g　　衛署藥輸字第022737號

【成 份】
每劑含主成分mesalazine 1 公克。
詳細賦形劑，請見【賦形劑】。

【劑型】
栓劑
外觀: 白色至黃褐色，帶有斑點之橢圓形栓劑。

【適應症】
輕度至中度潰瘍性直腸炎。

【用法及用量】
本藥須由醫師處方使用。
用量
每次1g (1 劑)，一天1-2 次。

兒童族群:
目前對於此族群僅有少數的相關使用經驗及有限的臨床文獻，故仍不建議使用。

使用方法
1. 建議使用前請先如廁。
2. 沿撕裂處打開鋁箔袋。
3. 將本栓劑塞入直腸直到感覺有阻力為止。
4. 為幫助更容易塞入直腸，本劑可搭配潤滑劑使用。
5. 如果本劑在塞入10 分鐘內排出，可以投予另一劑。

【禁忌】
PENTASA® suppositories 不可用於下列病人:
(1) 對mesalazine、藥品中任何賦形劑或salicylates過敏者。
(2) 有嚴重肝或腎功能不全病人。

【警語及注意事項】
大部分對sulphasalazine有不耐症或過敏的病人使用Pentasa®不會產生相似副作用的風險。然而，對sulphasalazine過敏的病人 (對salicylates有過敏的風險) 建議要小心使用本品。曾通報與mesalazine治療相關的嚴重皮膚不良反應包括史帝文生氏-強生症候群 (Stevens-Johnsons syndrome, SJS)和毒性表皮溶解症 (TEN)，當出現急性不耐症如腹絞痛、急性腹痛、發燒和劇烈頭痛及/或首次出現嚴重皮膚反應的症狀，例如皮疹時、黏膜病變或任何其他過敏反應症狀時，應立即停止治療。

對肝功能不全的病人建議要小心使用。根據醫師的評估，病人需在治療前和治療中接受對肝功能指數如ALT或AST的檢測。

有腎功能不全的病人，不建議使用本品。應定期檢測腎功能 (例如血清肌酸酐)，特別是治療初期。醫師須針對病人在治療前及治療中之尿液狀態 (尿液測量試紙) 進行評估。在治療期間，若病人出現腎功能異常時，應懷疑可能是mesalazine 引起之腎毒性造成。如果同時使用其他具腎毒性的藥物，需增加腎功能檢測的頻率。

有肺功能損傷的病人，尤其是氣喘病人，在治療期間須要非常小心的監測，請參閱【副作用】。

由mesalazine引起的心臟過敏反應（心肌炎及心包膜炎）的報告非常罕見。使用mesalazine出現的嚴重血液疾病的報告亦非常罕見。根據醫師的評估，建議在治療前及治療中作不同的血球計數的血液檢測。如標示在【藥物交互作用】一節，在接受azathioprine、6-mercaptopurine或thioguanine治療的病人，併用mesalazine治療可能增加發生血液疾病的危險性。如果懷疑或已發生上述不良反應則必須停止以本品治療。

發炎性腸道疾病的病人有發生腎結石的風險，在mesalazine治療期間曾通報過含mesalazine的腎結石案例。治療期間必須確保攝取充分的液體。

建議在併用治療後持續追蹤治療反應14天，之後以4週作為一個循環，追蹤2至3次。若一切正常，則改為每3個月追蹤一次。若出現其他症狀，則應立即採取進一步的臨床評估。

2歲以下的小孩不建議使用本品。

【藥物交互作用】
在一些試驗中顯示合併使用Pentasa®和azathioprine或6-mercaptopurine或thioguanine會有較高的骨髓抑制作用發生率，無法排除存在藥物交互作用的可能，但是這個交互作用的機轉尚未完全建立。建議定期監測白血球，同時thiopurines的使用劑量需要調整。

曾有報告指出，mesalazine可能降低warfarin抗凝血之功能，但目前證據尚不充足。

【生殖、懷孕、哺乳】
Pentasa® 使用於孕婦及哺乳婦女時應小心，而且只有在醫師評估潛在益處大於可能的危險性時方可使用。

懷孕
Mesalazine可以通過胎盤屏障，其在臍帶的濃度比母體血液的濃度低。代謝物acetyl-mesalazine在臍帶中的濃度與母體相似。口服mesalazine的動物試驗並無顯示對懷孕、胚胎發育、分娩或產後發育有直接或間接的傷害。目前尚無懷孕婦女服用Pentasa®之適當且控制良好之研究。有限的數據指出mesalazine不會增加胎兒先天性畸形的機率。雖曾有一些數據顯示早產、死產及新生兒出生體重較低的比例增加；但是，這些副作用也可能與腸炎疾病有關。
曾有報告顯示，懷孕時使用Pentasa®治療後，新生兒患有血液疾病 (全血球減少症、白血球缺乏症、血小板減少症、貧血)。

哺乳
Mesalazine 會分泌於乳汁中。在乳汁中mesalazine的濃度低於母體血中，而乳汁中代謝物acetyl-mesalazine 的濃度與母親血液相同或更高。未曾執行在哺乳期間使用Pentasa®的對照試驗。無法排除本藥可能引起新生兒過敏反應 (如腹瀉)。如果新生兒有腹瀉現象，應停止哺乳。

生殖
經由動物試驗顯示，mesalazine不會影響男性與女性之生殖能力。

【對開車及操作機器的能力】
使用Pentasa®治療不太可能會影響駕駛和操作機械的能力。

【副作用】
臨床試驗中最常見的副作用為腹瀉、噁心、腹痛、頭痛、嘔吐及皮疹。
偶而會發生過敏反應和藥物熱，即曾通報與mesalazine治療有關的嚴重皮膚不良反應包括史帝文生氏-強生症候群(SJS)和毒性表皮溶解症(TEN)，請參閱【警語及注意事項】。
直腸給藥後可能會出現一些局部反應例如搔癢、直腸不舒服和排便感。

根據臨床試驗和上市後監視，副作用發生的頻率如下：

MedDRA 組織分類	常見 (≥1/100 to <1/10)	罕見 (≥1/10,000 to <1/1,000)	非常罕見 (<1/10,000)	未知 (無法從現有的數據估計)
血液和淋巴系統			血球數目的改變 (貧血、再生不良性貧血、顆粒性白血球缺乏症、嗜中性白血球過少症、白血球減少 (包括顆粒性白血球過少症)、全部血球減少症、血小板減少症、嗜伊紅性白血球增多 (過敏反應的一部分))	
免疫系統			過敏反應、嚴重過敏反應、伴隨嗜伊紅性白血球增加與全身症狀的藥物反應 (DRESS[1])	
神經系統	頭痛	暈眩	周圍神經炎	
心臟		心肌炎*、心包炎*		
呼吸道、胸腔和縱膈膜			肺部過敏和纖維化反應 (包括呼吸困難、咳嗽、支氣管痙攣、過敏性肺	

			泡、肺嗜伊紅性白血球增多、間質性肺病、肺部浸潤、肺炎)	
胃腸道	腹瀉、腹痛、噁心、嘔吐、脹氣	澱粉酶增加、急性胰臟炎*	全結腸炎	
肝臟和膽道			轉氨酶增加、膽汁鬱滯參數增加 (例如鹼性磷酸酶 (ALP)、丙麥胺酸轉移酶 (GGT)、膽紅素)、肝毒性 (包括肝炎*、膽汁鬱滯性肝炎、肝硬化、肝衰竭)	
皮膚和皮下組織	皮疹 (包括蕁麻疹、紅斑性皮疹)	光敏性**	可逆性的禿髮、過敏性皮膚炎、多形性紅斑	史帝文生氏-強生症候群(SJS)/ 毒性表皮溶解症 (TEN)
肌肉骨骼、結締組織和骨骼			肌肉疼痛、關節痛、類紅斑性狼瘡症狀 (全身性紅斑性狼瘡)	
腎臟和尿道			腎功能損傷(包括急性和慢性間質性腎炎*、腎病症候群、腎功能不足)、尿液變色	腎結石***
生殖系統			精蟲稀少 (可逆性)	
一般疾病和投予部位	僅發生於直腸栓劑：肛門不適與給藥處刺激、肛門搔癢、直腸裡急後重之後墜感			

(+) DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
(*) Mesalazine 引發心肌炎、心包炎、胰臟炎、腎炎、肝炎的機制仍未 知，但是可能根源於過敏。
(**)光敏性:大部分發生此嚴重副作用之病人為本身即罹患先天的皮膚問題，例如異位性皮膚炎及過敏性濕疹。
(***) 詳細資訊請參閱【警語及注意事項】

必須考慮其中的一些疾病可能起因於發炎性腸道疾病本身。

【過量】

動物急性經驗：

給予豬隻單一口服mesalazine 劑量高達5g/kg 或是單一靜脈注射老鼠920mg/kg 的mesalazine 並不會致死。

人類經驗：

從有限的臨床經驗顯示過量的Pentasa®不會造成腎或肝毒性。因為Pentasa®屬於胺基水楊酸，故可能出現水楊酸類藥物毒性的症狀。

有報告指出病人每天服用8g的劑量持續一個月，無出現不良反應。

尚無針對過量治療之解毒劑或藥物，一般採取症狀處理。在醫院之治療包含密切監控腎臟功能。

【藥物藥效學】

藥物治療學分類: :腸道抗發炎製劑 (A07 EC02)

作用機轉及藥物藥效動力學作用: mesalazine是sulfasalazine的活性成分，主要用來治療潰瘍性結腸炎。
根據臨床結果，mesalazine直腸給藥的治療效能是作用於局部的發炎腸道組織，而非全身性作用。有資訊指出潰瘍性直腸炎病人使用mesalazine所造成的結腸炎程度與腸黏膜內的mezalamine濃度呈反比。

在IBD病人身上可見到白血球轉移增加、異常細胞激素產生、花生四烯酸 (arachidonic acid) 代謝物增加，特別是白三烯B4 (leukotriene B4) 及發炎腸道組織自由基生成增加。儘管腸黏膜內過氧化體增生活化受體 γ-form (PPAR-γ) 的活化及核轉錄因子κB (NF-κB) 的抑制機制似乎與mesalazine的作用機轉相關，但mesalazine的詳細作用機轉仍尚未完全清楚。Mesalazine在體外和體內藥理作用有抑制白血球的化學趨化作用、降低細胞素和白三烯的產生及清除自由基。目前仍未知在臨床上哪一個是mesalazine的主要作用機轉。

【藥物動力學】

活性成分之特性

作用位置和局部效果:

Mesalazine治療效果最有可能是取決於藥物與腸黏膜病灶的局部接觸。

Pentasa®栓劑是為腸道末端提供高濃度的mesalazine和降低全身性吸收而設計，並可覆蓋全直腸。

吸收:

直腸給藥的吸收很低，且與劑量、劑型和分布擴散有關。根據健康志願者回收之尿液數據，給予每日 2g (1gx2) 的栓劑約 10%劑量被吸收。

分佈:

Mesalazine蛋白結合率約50%，acetyl-mesalazine約80%。

代謝:

Mesalazine在進入全身系統前在小腸黏膜，和進入全身系統後在肝臟，主要被第一型乙醯轉化酶 (NAT-1)代謝為N-acetyl-mesalazine (acetyl-mesalazine)。也有一些乙醯化是由結腸的細菌產生。乙醯化似乎與病人乙醯化表現型無關。

排除:

純mesalazine血中半衰期約40分鐘，而acetyl-mesalazine約70分鐘。

【臨床前安全性資料】

在所有試驗的動物身上已證實有腎毒性，老鼠和猴子的劑量和血中濃度在無觀察危害反應劑量是人類2-7.2倍。
動物試驗顯示無明顯與胃腸道、肝臟或造血系統有關的毒性。

體外和體內試驗顯示無致突變或染色體損毀的發生。在大鼠和小鼠的致腫瘤試驗顯示無證據與任何腫瘤發生的增加有關。

口服mesalazine的動物試驗並無顯示對生殖、懷孕、胚胎發育、分娩或產後發育有直接或間接的傷害。

Mesalazine在病人使用的劑量下，不會對環境造成危害。

【賦形劑】

Magnesium stearate、talc、povidone、macrogol 6000

【有效期限】

請參閱外包裝

【儲存】

儲存於30°C 以下，請置於原包裝內避光保存。

【包裝】

每片雙面鋁箔blister包裝，含有7片栓劑，每盒有四片鋁箔blister共28劑。

【丟棄時注意事項】

無特別要求。
任何未使用的藥品或廢棄物須遵照當地要求進行處理。

製造廠: Ferring International Center SA
Chemin de la Vergognausaz 50, CH-1162 Saint Prex, Switzerland
藥商: 輝凌藥品股份有限公司
地址: 台北市中山區松江路 111 號 11 樓
電話: (02) 2515-8277

PENTASA® Suppositories 1 g

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each suppository contains 1 g mesalazine.
For a full list of excipients, see section LIST OF EXCIPIENTS.

PHARMACEUTICAL FORM
Suppository
Appearance of PENTASA® suppositories: White to tan, spotted, oblong suppositories.

THERAPEUTIC INDICATIONS
Treatment of ulcerative proctitis.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
1 suppository 1-2 times daily.

Paediatric population:
There is little experience and only limited documentation for an effect in children.

Method of administration
1. A visit to the toilet is recommended before administration of suppositories.
2. Open the foil bag at the tear mark.
3. The suppository is inserted in the rectum until resistance is felt and disappeared again.
4. In order to facilitate the administration, the suppository can be moistured with water or moisture cream.
5. If the suppository is discharged within the first 10 minutes, another can be inserted.

CONTRAINDICATIONS
Hypersensitivity to mesalazine, any of the excipients, or salicylates.
Severe liver or renal impairment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Most patients who are intolerant or hypersensitive to sulphasalazine are able to take PENTASA® without risk of similar reactions. However, caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever and severe headache and/or the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other signs of hypersensitivity, therapy should be discontinued immediately.

Caution is recommended in patients with impaired liver function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.

The drug is not recommended for use in patients with renal impairment. The renal function should be monitored regularly (e.g. serum creatinine), especially during the initial phase of treatment. Urinary status (dip sticks) should be determined prior to and during treatment at the discretion of the treating physician. Mesalazine induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The concurrent use of other known nephrotoxic agents should increase monitoring frequency of renal function.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely. Serious blood dyscrasias have been reported very rarely with mesalazine. Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. As stated in section INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION, concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving azathioprine, or 6-mercaptopurine or thioguanine. Treatment should be discontinued on suspicion or evidence of these adverse reactions.

Patients with inflammatory bowel disease are at risk of developing nephrolithiasis. Cases of nephrolithiasis with mesalazine content have been reported during treatment with mesalazine. Adequate fluid intake must be ensured during treatment.

As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional symptoms occur, these tests should be performed immediately.

Care should be taken in children below 2 years.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Combination therapy with PENTASA® and azathioprine, or 6-mercaptopurine or thioguanine have in several studies shown a higher frequency of myelosuppressive effects, and an interaction seems to exist, however, the mechanism behind the interaction is not fully established. Regular monitoring of white blood cells is recommended and dosage regime of thiopurines should be adjusted accordingly.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

FERTILITY, PREGNANCY AND LACTATION

PENTASA® should be used with caution during pregnancy and lactation and only if the potential benefits outweigh the possible hazards in the opinion of the physician.

Pregnancy

Mesalazine is known to cross the placental barrier and its concentration in umbilical cord plasma is lower than the concentration in maternal plasma. The metabolite acetyl-mesalazine is found at similar concentrations in umbilical cord and maternal plasma. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, parturition or postnatal development. There are no adequate and well-controlled studies of PENTASA® use in pregnant women. Limited published human data on mesalazine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease.

Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with PENTASA®.

Breastfeeding

Mesalazine is excreted in breast milk. The mesalazine concentration in breast milk is lower than in maternal blood, whereas the metabolite-acetyl-mesalazine-appears in similar or increased concentrations. No controlled studies with PENTASA® during breast-feeding have been carried out. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. If the infant develops diarrhoea, breast-feeding should be discontinued.

Fertility

Animal data on mesalazine show no effect on male and female fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Treatment with PENTASA® is unlikely to affect the ability to drive and/or use machines.

UNDESIRABLE EFFECTS

The most frequent adverse reactions seen in clinical trials are diarrhoea, nausea, abdominal pain, headache, vomiting, and rash.

Hypersensitivity reactions and drug fever may occasionally occur and severe cutaneous adverse reactions, including SJS and TEN, have been reported in association with mesalazine treatment (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Following rectal administration local reactions such as pruritus, rectal discomfort and urge may occur.

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance

MedDRA Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Altered blood counts (anaemia, aplastic anaemia, agranu-locytosis, neutropenia, leukopenia (including granulocytopenia), pancytopenia, thrombocytopenia, and eosinophilia (as part of an allergic reaction)	

MedDRA Organ Class	Common (≥1/100 to <1/10)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity reaction including anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	
Nervous system disorders	Headache	Dizziness	Peripheral neuropathy	
Cardiac disorders		Myo*- and pericarditis*		
Respiratory, thoracic and mediastenal disorders			Allergic and fibrotic lung reactions (including dyspnoea, coughing, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)	
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea, vomiting, flatulence	Increased amylase, acute pancreatitis*	Pancolitis	
Hepato-biliary disorders			Increase in transaminases, increase in cholestasis parameters (e.g. alkaline phosphatase, gamma - glutamyltransferase and bilirubin),hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)	
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Photosensitivity**	Alopecia reversible, dermatitis allergic, erythema multiforme	Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders			Myalgia, arthralgia, lupus erythematosus-like syndrome (systemic lupus erythematosus)	
Renal and urinary disorders			Renal function impairment (incl. acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency), urine discolouration	Nephrolithiasis ***
Reproductive system disorders			Oligospermia (reversible)	
General disorders and administration site conditions	Only with rectal form: Anal discomfort and irritation at the application site, pruritus (anal), rectal tenesmus		Drug fever	

(↓) DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

(*) The mechanism of mesalazine-induced myo- and pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

(**) Photosensitivity: More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

(***) See section SPECIAL WARNINGS AND PRECAUTIONS FOR USE for further information.

It is important to note that several of these disorders can also be attributed to the inflammatory bowel disease itself.

OVERDOSE

Acute experience in animals:
Single oral doses of mesalazine up to 5 g/kg in pigs or a single intravenous dose of mesalazine at 920 mg/kg in rats were not lethal.

Human experience:
There is limited clinical experience with overdose of PENTASA® which do not indicate renal or hepatic toxicity. Since PENTASA® is an amino salicylate, symptoms of salicylate toxicity may occur.

There have been reports of patients taking daily doses of 8 grams for a month without any adverse events.

There is no specific antidote and the management of overdose is supportive and symptomatic. The treatment at the hospital includes close monitoring of renal function.

PHARMACODYNAMICS PROPERTIES
Pharmacotherapeutic group: Intestinal anti-inflammatory agents (A07 EC02).

Mechanism of action and pharmacodynamic effects: It has been established that mesalazine is the active component of sulfasalazine, which is used for the treatment of ulcerative colitis.
Based on clinical results, the therapeutic value of mesalazine after rectal administration appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mezalamine.

Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4, and increased free radical formation in the inflamed intestinal tissue are all present in patients with IBD. The mechanism of action of mesalazine is not fully understood although mechanisms such as activation of the γ-form of peroxisome proliferator-activated receptors (PPAR-γ) and inhibition of nuclear factor-kappa B (NF-κB) in the intestinal mucosa has been implicated. Mesalazine has in-vitro and in-vivo pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leucotriene production, and scavenge for free radicals. It is currently unknown which, if any, of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

PHARMACOKINETICS PROPERTIES
General characteristics of the active substance
Disposition and local availability:
The therapeutic activity of mesalazine most likely depends on a local contact of the drug with the diseased area of the intestinal mucosa.
PENTASA® suppositories are designed to provide the distal part of the intestinal tract with high concentrations of mesalazine and a low systemic absorption. Suppositories cover the rectum.

Absorption:
The absorption following rectal administration is low, and depends on the dose, the formulation and the extent of spread. Based on urine recoveries in healthy volunteers under steady-state conditions given a daily dose of 2g (1g x 2), approximately 10% of the dose is absorbed after administration of suppositories.

Distribution:
Protein binding of mesalazine is approximately 50% and of acetyl-mesalazine about 80%.

Metabolism:
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl-mesalazine (acetyl-mesalazine) principally by NAT-1. Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient.

Elimination:
The plasma half-life of pure mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes.

PRECLINICAL SAFETY DATA
Toxic renal effects have been demonstrated in all species tested. Rat and monkey dosages and plasma concentrations at the No Observed Adverse Effect Levels (NOAELs) exceed those used in humans by a factor of 2-7.2.
No significant toxicity associated with the gastrointestinal tract, liver or haematopoietic system in animals has been observed.

In vitro test systems and in-vivo studies showed no evidence of mutagenic or clastogenic effects. Studies of the tumourigenic potential carried out in mice and rats showed no evidence of any substance-related increase in the incidence of tumours.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

Mesalazine is deemed not to pose a risk to the environment at the doses prescribed for usein patients.

LIST OF EXCIPIENTS
Magnesium stearate, talc, povidone, macrogol 6000

SHELF-LIFE
Please see the package.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Store in the original package, as the product is sensitive to light.

NATURE AND CONTENTS OF CONTAINER
Double aluminium foil blisters. Box of 28 suppositories.

SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements.

MANUFACTURER
Ferring International Center SA
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