N1223802E

Merck Serono

MERCK

帥健®注射劑12毫克

saizen® 12 mg solution for injection

帥健®注射劑20毫克

saizen® 20 mg solution for injection

本藥限由醫師使用

Saizen® 12 mg Solution for Injection　衛署菌疫輸字第000932號

Saizen® 20 mg Solution for Injection　衛署菌疫輸字第000933號

組成

帥健®注射劑8毫克/毫升。每支藥匣含有1.50毫升溶液（12毫克Somatropin*）或2.50毫升溶液（20毫克Somatropin*）。

*基因重組人類生長激素乃利用哺乳動物細胞以基因重組技術製造而成。

賦形劑：Sucrose, Poloxamer 188, Phenol, Citric Acid 2.5%, Citrate Buffer 10 mM

劑型

注射液。

澄清至淡乳白色的溶液，pH值為5.6-6.6，滲透壓為250-450 mOsm/kg。

適應症

孩童及青少年：

- 腦下垂體生長激素分泌不足所導致之生長遲滯
- 其他Gonadol Dysgenesis（Turner's syndrome）所導致之生長遲滯
- 青春期前因慢性腎臟衰竭導致之生長遲滯
- 低出生體重兒（Small for Gestational Age; SGA)逾四歲者之生長障礙

  說明：低出生體重兒（small for gestational age, SGA）之生長障礙（目前的身高標準差評分 [SDS] < -2.5且經校正父母親的身高後其身高SDS仍小於-1），照姓娠週數來看，他們生來個子就很小（體重或身長低於-2SD），到四歲或更大時生長仍未趕上同齡兒童（最近一年內HV SDS < 0）。

成人：

- 成人生長激素嚴重分泌不足之補充療法

  說明：成人生長激素嚴重分泌不足之補充療法需經診斷後證實為生長激素缺乏。患者需符合下列條件：

  孩童時期發生：在孩童時期即診斷為生長激素分泌不足者，在成年後繼續生長激素補充療法前需再次檢查，確定生長激素仍分泌不足。

  成人時期發生：開始生長激素補充療法前需經診斷為因下視丘或腦下垂體疾病造成的生長激素分泌不足及至少一種荷爾蒙缺乏（除prolactin）診斷確定，在適當的取代治療前使用生長激素。

用法用量

Saizen® 8 mg/ml為供單一患者使用的多劑量藥物。

一般建議應於晚上睡前注射，並以下列劑量使用：

孩童及青少年：

用量依患者個別的體表面積或體重計算注射劑量。

- 因內生性生長激素分泌不足引起的生長遲滯：每天以0.7~1.0毫克/平方公尺體表面積或0.025~0.035毫克/公斤體重皮下注射。
- 其他Gonadol Dysgenesis（Turner syndrome）所導致之生長遲滯：每天以1.4 mg/平方公尺體表面積或0.045~0.050 mg/公斤體重皮下注射。若同時使用non-androgenic anabolic steroids，將會增加治療效果。
- 青春期前因慢性腎臟衰竭導致之生長遲滯：每天以1.4 mg/平方公尺體表面積或0.045~0.050 mg/公斤體重皮下注射。
- 低出生體重兒之生長遲緩：每天給予0.035 mg/公斤體重（或1 mg/平方公尺體表面積/每天，相當於0.1 IU/公斤體重/每天或3 IU/平方公尺體表面積/每天）皮下注射。

當身高達到理想之成人高度或骨骺已閉合時，應停止治療。

治療低出生體重兒之生長遲緩，治療通常持續至該孩童達到最終高度為止。若治療的第一年生長速率低於1個標準差評分，則應停止治療。當孩童達到最終高度（每年生長速率小於2公分）且需要時經確認其骨齡已達骨骺閉合年齡（女生大於14歲或男生大於16歲）時，應停止治療。

成人：

- 成人生長激素嚴重分泌不足之補充療法

  開始治療時，建議每日以0.15~0.3 mg低劑量皮下注射治療。治療劑量可依Insulin-like Growth Factor 1（IGF-1）值逐步調整。最終建議劑量很少超過1.0 mg/每天。一般而言只需使用最低有效劑量。如果使用者為老人或體重過重者，應選擇較低劑量使用。

Saizen®藥品調配用法，請詳閱藥品仿單說明（參見使用方法/藥品調配方法）及參照挑選的auto-injector: cool.click® needle-free auto-injector或Easypod auto-injector使用說明書。

Easypod的自行操作者主要為7歲以上的兒童及成人。兒童使用本注射器時，應在大人的監督下使用。

藥物的製備說明請參閱“丟棄及其他處理方式之注意事項”。

禁忌

- 對somatropin或其賦形劑過敏者。
- 骨骺已經閉合的兒童不可使用somatropin促進其生長。
- Somatropin禁用於有活動性贅瘤或/和活動性或進行性的顱內損傷或復發。
- 因開心手術、腹腔手術、意外造成多處外傷、急性呼吸衰竭或類似情形導致發生嚴重疾病時，應停止使用Somatropin。
- 患有慢性腎臟病的兒童在接受腎臟移植時，somatropin必須停藥。
- 在顱內腫瘤發生初期，少數案例會以生長激素缺乏為表徵，治療前應排除此類腫瘤可能性。開始somatropin治療時，任何已存在的腫瘤應為不活動性，且任何抗腫瘤治療需在開始somatropin治療前完成。

警語及注意事項

治療需由對生長激素缺乏症領域有經驗的醫師使用。

勿使用超越每日最大建議劑量。（參考用法用量）

若接受生長激素治療時，患者有顱內或顱外的贅瘤，則需由醫師定期監測。

如因腦瘤引起的生長激素缺乏，治療時應接受定期檢查。

報告指出，第一次腫瘤治癒後的孩童癌症病患，於接受somatropin治療後，發生第二次腫瘤的風險將提高。過去曾接受頭部放射線治療以治療腫瘤的病患，最可能發生第二次的腫瘤為顱內腫瘤，特別是腦膜腫瘤。

普瑞德威利氏症候群（Prader-Willi syndrome）

從遺傳學上已確認為普瑞德威利症候群之病童，其生長遲滯不會使用somatropin進行長期治療，但若這些患者也有生長激素缺乏的情形則除外。普瑞德威利症候群之病童在接受生長激素治療後，曾發生睡眠呼吸停止及猝死的報告，這些病童都帶有下列一項或多項危險因子：嚴重肥胖、上呼吸道阻塞或睡眠呼吸停止的病史，或未經確認的呼吸道感染。

白血病

在接受somatropin治療之生長激素缺乏的患者，有少數白血病的個案曾發生。然而，對於無易患因子（predisposing factors）的患者，並無證據顯示其接受生長激素治療會提高白血病的發生機率。

胰島素的敏感度

因為somatropin會降低胰島素的敏感度，因此應監測患者是否出現葡萄糖不耐症。糖尿病患者在開始接受含有somatropin的藥物治療後應調整胰島素的劑量。糖尿病患者或葡萄糖耐受性不良的患者在somatropin治療期間應予以嚴密監測。

視網膜病變穩定無惡化的情況下無須停止生長激素治療。若視網膜病變情形惡化或加重，應停止生長激素治療。

甲狀腺功能

生長激素會使週邊的T4轉換成T3，在這種情況下，可能會觀察到早期的甲狀腺功能低下症。若正服用甲狀腺素治療，則可能發生輕微甲狀腺功能亢進。甲狀腺功能應在Saizen®開始治療前先行評估，並於治療期間定期檢查，一年至少一次。若在Saizen®治療期間被診斷出甲狀腺功能低下症，則應調整Saizen®劑量以矯正甲狀腺功能。

當腦下垂體功能低下的患者接受somatropin時，應嚴密監測標準替代治療（standard replacement therapy）。

良性顱內高壓

Saizen®開始治療前應定期進行眼底鏡檢查，以排除先前已存在的視乳突水腫，若臨床上有任何懷疑則應重覆進行檢查（例如有嚴重或復發性頭痛、視力問題、噁心及/或嘔吐的情況發生）。如經由眼底鏡確定有視乳突水腫則應注意是否有良性顱內壓升高（或大腦假性腫瘤[pseudotumor cerebri]）的情況並停止使用Saizen®。目前並無對顱內壓上升的處置規範。若重新投予生長激素，應小心監測顱內高壓的症狀。如果再度上升，則需停止使用生長激素。

胰臟炎

發生案例罕見，但接受somatropin治療的病患應注意發生胰臟炎的可能，特別是有腹痛症狀的孩童。

抗體

如同所有含somatropin的藥品一樣，少數病人會對somatropin產生抗體。這些抗體的鍵結能力低，因此不會影響生長速率。若患者對治療沒有反應，則應對somatropin的抗體進行測試。

患有內分泌性疾病，包括生長激素缺乏、甲狀腺功能低下患者，在急速生長時常伴隨股骨頭骺脫滑的現象。使用生長激素的孩童發生股骨頭骺脫滑，其原因可能是潛在的內分泌失調或治療產生的急速生長所導致。急速生長通常伴隨關節問題，股骨頭因青春期前快速生長過度使用而損傷。醫師及患者應了解使用Saizen®可能會發生跛行或髖部、膝蓋疼痛的感覺。

因慢性腎衰竭導致之生長遲滯患者應定期接受檢查以了解腎性骨發育不全的進展情況。進階性腎性骨發育不全的兒童可能會有股骨頭骺脫滑或股骨頭無血性壞死現象發生，但不知是否與生長激素有關。在治療前應接受髖部X-ray檢查。

慢性腎衰竭兒童在治療前的腎功能已降至正常值之50%以下，為證明生長速度受到影響，必須先檢查一年內的成長情況。對於腎功能不足的治療（包括治療一年前開始進行的控制酸毒症、副甲狀腺素機能過旺及營養狀況）必須持續進行。如果進行腎臟移植時，應停止生長激素治療。

治療低出生體重兒之生長遲緩前，應排除其他藥物或治療所導致之生長遲緩。

治療低出生體重兒之生長遲緩前，應監測空腹之胰島素及血糖值，之後每年定期監測。針對糖尿病高危險群（家族性糖尿病、肥胖、BMI過高、嚴重胰島素抗阻性或黑棘皮症），應進行口服葡萄糖測試，若發現有糖尿病，不應使用生長激素。

治療低出生體重兒之生長遲緩前，建議監測血中IGF-1數值，之後每年定期檢查兩次。若有兩次以上檢查證實IGF-1數值大於孩童年齡標準值或青春期的2個標準分數，必須考慮以IGF-1/IGFBP-3比值調整治療劑量。

在青春期的起始點才開始治療低出生體重兒之生長遲緩的經驗有限，因此不建議使用於此類病人。使用於合併有Silver-Russell syndrome的經驗也有限。

因身材矮小而使用生長激素治療低出生體重兒，若在達到最終身高之前即停止用藥，先前治療所得到的生長高度可能會失去意義。

成人接受生長激素替代治療期間可能會出現預期中的體液滯留現象。

若出現持續性水腫或嚴重的感覺異常，則應降低劑量以避免腕隧道症候群（carpal tunnel syndrome）的發生。

應在不同的注射部位輪流注射以避免注射部位局部脂肪組織萎縮。

成人生長激素分泌不足需終身的治療，但在大於六十歲以上或長期使用的資料仍有限。

治療期間如有急性嚴重疾病發生，應衡量生長激素治療效益與潛在危險以決定是否繼續使用。

藥物交互作用

併用glucocorticoids治療會抑制含有somatropin藥物對生長刺激的作用。促腎上腺皮質素（ACTH）缺乏的患者在接受glucocorticoids替代療法時，應小心調整劑量以避免生長激素的作用受到抑制。

此外，某些患者在開始生長激素替代療法時可能會因為較低的11β-hydroxysteroid dehydrogenase, type 1（11β-HSD1）活性而造成續發性腎上腺功能不足。11β-HSD1是一種酵素，能將不活化的cortisone轉變成cortisol。使用glucocorticoid替代療法的患者在開始使用somatropin時，可能會造成cortisol缺乏。因此可能需要調整glucocorticoid的劑量。

由於口服oestrogens可能會降低somatropin治療中患者血清中IGF-1的反應，因此使用口服oestrogens替代療法的患者可能需要較高的somatropin劑量。

針對生長激素缺乏的成人所做的交互作用研究顯示，somatropin可能會使經由肝臟代謝酵素cytochrome P450同功酶代謝之藥物的清除率提高。經由肝臟代謝酵素cytochrome P450 3A4代謝之藥物（例如，性荷爾蒙、皮質類固醇、抗癲癇藥及cyclosporin）的清除率可能會增加特別多，因而導致其血漿濃度下降。這在臨床上的意義則尚不清楚。

懷孕與授乳

懷孕：

根據含有somatropin的藥物對動物所做的生殖研究看來，並無證據顯示其會增加對胚胎或胎兒不良反應的風險。目前尚無somatropin使用於懷孕動物的資料（見臨床前安全性資料）。因此，含有somatropin的藥物不建議使用於懷孕期間的婦女及沒有採取避孕措施的育齡期婦女。

授乳：

目前尚無針對授乳婦女接受somatropin治療所做的臨床研究。Somatropin是否會分泌於人類乳汁中亦不清楚。因此授乳婦女使用somatropin時應小心。

對開車及操作機械的影響

含有somatropin的藥物不會影響開車及操作機械的能力。

不良反應

約10%的患者在注射部位會有紅腫、搔癢的情況發生，特別是以皮下注射方式注射時。

接受生長激素治療的成人，體液滯留現象的發生是可預期的。臨床上體液滯留症狀可能包括：浮腫、關節腫大、關節痛、肌肉痛或皮膚感覺異常等。這些症狀通常為暫時性且與劑量相關。

在孩童時期即診斷為生長激素分泌不足者，其副作用發生比例較成人時才診斷出者低。

少數患者會對Somatropin產生抗體。抗體對於臨床上的影響未知，抗體雖會降低生長激素的結合力，但除非是基因缺失的患者，抗體並不會影響療效。極少數的病例中，患者生長遲滯是由於生長激素基因缺失所造成，如果以生長激素治療則可能會產生減少生長效果的抗體。

生長激素缺乏的患者曾有少數發生白血病的報告，這其中有些患者為接受somatropin之治療。然而，對於無易患因子（predisposing factors）的患者，並無證據顯示其接受生長激素治療會提高白血病的發生機率。

於上市後研究曾發生使用生長激素治療後有胰臟炎之案例。

在每一個發生頻率組別中，不良反應的排列順序是以嚴重度遞減的方式呈現。

依器官系統分類	常見（≥1/100, <1/10）	不常見（≥1/1,000, <1/100）	非常罕見（<1/10,000）	頻率不明
中樞神經系統疾病	頭痛（單一性的） 腕隧道症候群（成人）	自發性顱內高壓（良性顱內高壓）， 腕隧道症候群（兒童）		
肌肉骨骼及結締組織系統疾病			股骨頭骺脫滑（股骨頭脫位）或股骨頭無血性壞死	
免疫系統疾病				局部與全身性過敏反應
內分泌系統疾病			甲狀腺功能低下症	
代謝及營養疾病	成人： 體液滯留：週邊水腫、僵硬、關節痛、肌肉痛和皮膚感覺異常	孩童： 體液滯留：週邊水腫、僵硬、關節痛、肌肉痛和皮膚感覺異常		胰島素耐受性可能導致胰島素過多症和少數的高血糖症
生殖系統與乳房疾病		男性 女乳症		
全身性疾病及注射部位反應	注射部位反應： 局部脂肪組織萎縮（經常改變注射部位可預防其發生）			
腸胃道疾病				胰臟炎

注射過量

並無急性過量之案例發生。使用超過建議用量的藥品，則可能造成副作用。過量時可能導致血糖值降低繼之以血糖值升高。此外，注射過量有可能呈現出體液滯留現象。

藥理學特性

藥理分類：腦下垂體前葉荷爾蒙類似劑，ATC code：H01AC01

Saizen®含有以基因工程方式於哺乳類動物細胞中製備而得的重組人類生長激素。

它由191個氨基酸組成，其氨基酸排序、組成、氨基酸圖譜、等電點、分子量、同分異構構造與生物活性等皆與人類腦下垂體分泌之生長激素相同。

Saizen®由加入鼠科細胞經轉植腦下垂體生長激素的基因所合成的。

Saizen®是一種同化及抗異化劑，不僅可促進生長也可改變體組成及代謝。它可與各種的細胞包括肌細胞、肝細胞、脂肪細胞、淋巴細胞、造血細胞上的專一性接受器結合，它的部分作用是經由介質somatomedins（IGF-1、IGF-2）達成。

依劑量不同，使用Saizen®可誘導IGF-1、IGFBP-3、非酯化脂肪酸及甘油上升、降低血中尿素、尿中含氮量及鈉、鉀的排出。生長激素濃度上升的時間長短可決定其造成的效果大小。若使用高劑量可能造成Saizen®作用效果的飽和現象。只有在使用高劑量（每次20 mg）才會出現血糖過多或C-胜肽排出。

一項隨機設計臨床試驗顯示，對於低出生體重、青春期前的孩童，每天給予0.067 mg/kg治療三年後，平均可獲得+1.8個標準分數的高度。若中斷治療三年以上，將損失部分治療所得的效益，但病患到最終高度時能維持+0.7個標準分數的高度（具統計意義，$p < 0.01$）。經不同長短時間的觀察期後，接受第二次療程的患者達到最終高度時平均獲得+1.3個標準分數（$p=0.001$）（累積的治療期平均為6.1年）。後組接受治療所得的平均標準分數的高度（+1.3±1.1）相較於前一組接受三年治療所得的平均標準分數的高度（+0.7±0.8），具有統計意義的差異（$p < 0.05$）。

另一項臨床試驗評估兩種不同方式的間斷式給藥治療法，一組每天給予0.067 mg/kg的劑量，持續使用2年後追蹤兩年；另一組在第一、第三年每天給予0.067 mg/kg的劑量，第二、第四年不給藥，四年後試驗終了時，兩組皆顯示生長速度加快，分別獲得+1.55個標準分數（$p < 0.0001$）及+1.43個標準分數（$p < 0.0001$）的結果。長期使用之安全性資料有限。

藥物動力學特性

使用Saizen® 8 IU（2.67 mg）以下的劑量，藥物動力學呈線性比例增加。使用高劑量（60 IU/20 mg）則不排除有非線性藥物動力學出現，但與臨床並無相關性。

健康受試者以IV注射Saizen®後，達到穩定期後之分佈體積為7公升，總代謝清除率為15公升/小時。腎臟清除率可忽略。藥品清除半衰期為20~35分鐘。

在單一劑量皮下或肌肉注射Saizen®時，最終半衰期較長約為2~4小時，這是因為速率限制吸收過程所造成。

以皮下或肌肉注射Saizen®其絕對生體可用率為70~90%。

注射Saizen®四小時後，達到血中最高生長激素濃度，在24小時內會回到基準線，顯示在重複投與後並不會造成體內生長激素蓄積的現象。

以皮下注射給藥的Saizen®注射劑（5.83及8.00 mg/ml）和8 mg凍晶配方具有生體相等性。

臨床前安全性資料

Saizen®注射劑以8.00 mg/ml的濃度及每個注射部位1 ml之劑量注射於動物時，可發現其局部耐受性佳且適合以皮下注射給藥。

根據傳統的藥理安全性研究、單劑量及多劑量之毒性研究，及遺傳毒性研究的非臨床資料顯示，本品對人類並無特殊危險。但並未進行正式的致癌性研究。這是考量蛋白質的特性，且其遺傳毒性檢測呈陰性反應所作的判定。基因重組人類生長激素（r-hGH）對於先前已存在的腫瘤之生長情況的潛在影響已進行體外及體內試驗評估，其結果顯示，基因重組人類生長激素並不會讓患者長出腫瘤或刺激原有的腫瘤。雖然使用劑量已足以產生生長藥理作用的劑量，生殖系統毒性試驗並無任何副作用發生。

不相容性

因為缺乏相容性的研究，本品不應與其他藥物混合使用。

儲存方法與條件

2年

從物理、化學與微生物的觀點來看，本品在使用中的安定性，可於2-8℃下維持28天；其中可達連續7天最高25℃。

其他關於使用狀態下的儲存時間及條件為使用者之責任。在首次注射後，Saizen® cartridge或是裝有Saizen® cartridge的easypod自動注射器必須存放在冰箱（2-8℃），最長達28天；其中離開冰箱可達連續7天最高25℃。當存放在冰箱以外達連續7天後，Saizen® cartridge必須回到冰箱，直到首次注射後的28天為止。不可冰凍。28天後剩餘的藥品必須丟棄。

儲存注意事項

藥品保存於2~8℃。不可冰凍。請置於原包裝盒中避光儲存。

當Eeasypod自動注射器裝入Saizen®藥匣，則必須一同儲存於冰箱（2℃-8℃）。當使用cool.click無針式自動注射器時，只需將Saizen®藥匣儲存於冰箱（2℃-8℃）。

包裝

藥品容器為無色第I類玻璃所製成的藥匣瓶，封口處為bromobutyl材質橡皮塞並套上有單層bromobutyl橡皮內層的鋁蓋。Saizen® 8 mg/ml注射液有下列幾種包裝：

1支裝：每支含1.50毫升溶液（12毫克somatropin）

1支裝：每支含2.50毫升溶液（20毫克somatropin）

丟棄及其他處理方式之注意事項

藥匣中包含Saizen® 8 mg/ml溶液，須與cool.click無針式自動注射器或Easypod自動注射器搭配使用。

含有藥匣之自動注射器的儲存方式請參見“儲存注意事項”。

注射劑必須為澄清至淡乳白色，不得有顆粒，也不可出現肉眼可見的變質徵兆。如果溶液中含有顆粒，請勿使用。

任何未使用完之藥品或廢棄物請依當地規定處置。

重要資訊

注射Saizen®前，請先詳細閱讀下列資訊。

本品長期注射於同一個部位可能會造成傷害。不斷更換注射部位是很重要的。您的醫師或藥師會告訴您適合注射的部位。請勿注射於可以感覺出腫塊、結節、凹陷或疼痛的任何部位；若您發現任何問題，請告訴您的醫師或藥師。注射部位應以肥皂及清水清潔之。

內含Saizen®注射劑的藥匣可配合cool.click無針式自動注射器或easypod自動注射器使用。

裝配注射劑所需的任何配件應放在清潔的桌面上，並以肥皂及清水洗淨的雙手操作之。

注射劑必須為澄清至淡乳白色，不得有顆粒，也不可出現肉眼可見的變質徵兆。若溶液中含有顆粒，則不可用於注射。

每日如何自行注射Saizen®

關於藥匣如何套上cool.click無針式自動注射器或easypod自動注射器，以及如何注射Saizen®注射劑，請詳細閱讀每種自動注射器所附上的使用說明書。

Easypod的自行操作者主要為7歲以上的兒童及成人。兒童使用本注射器時，應在大人的監督下使用。

資料日期

2017年4月；CCDS v3.0

製造廠：Merck Serono S.p.A
廠　址：Via Delle Magnolie 15, Zona Industriale di Modugno, 70026 Modugno, Italy
包裝廠：Merck Serono SA, Aubonne Branch.
廠　址：Zone Industrielle De l'Ouriettaz, 1170 Aubonne, Switzerland
藥　商：台灣默克股份有限公司
地　址：台北市內湖區堤頂大道二段89號6樓
電　話：（02）2162-1111

Merck Serono

MERCK

saizen®

12 mg solution for injection
20 mg solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Saizen 8 mg/ml solution for injection. Each cartridge contains 1.50 ml solution (12 mg somatropin*) or 2.50 ml solution (20 mg somatropin*).

* recombinant human growth hormone, produced by recombinant DNA technology in mammalian cells

Excipients: Sucrose, Poloxamer 188, Phenol, Citric Acid 2.5%, Citrate Buffer 10mM

PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent solution with pH of 5.6-6.6 and osmolality 250-450 mOsm/kg

CLINICAL PARTICULARS

Therapeutic indications

Saizen is indicated in the treatment of:

Children and adolescents:

- Growth failure in children caused by decreased or absent secretion of endogenous growth hormone.
- Growth failure in girls with gonadal dysgenesis (Turner syndrome), confirmed by chromosomal analysis.
- Growth failure in prepubertal children due to chronic renal failure (CRF).
- Growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA) with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later.

Adults:

- Replacement therapy in adults with pronounced growth hormone deficiency as diagnosed by a single dynamic test for growth hormone deficiency. Patients must also fulfil the following criteria:
  - Childhood onset:
    Patients who were diagnosed as growth hormone deficient during childhood, must be retested and their growth hormone deficiency confirmed before replacement therapy with Saizen is started.
  - Adult onset:
    Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin.

Posology and method of administration

Saizen 8 mg/ml is intended for multiple dose use in an individual patient.

It is recommended that Saizen be administered at bedtime according to the following dosage:

Children and adolescents:

Saizen dosage should be individualised for each patient based on body surface area or on body weight.

- Growth failure due to inadequate endogenous growth hormone secretion:
  0.7-1.0 mg/m2 body surface area per day or 0.025-0.035 mg/kg body weight per day by subcutaneous administration.
- Growth failure in girls due to gonadal dysgenesis (Turner Syndrome):
  1.4 mg/m2 body surface area per day or 0.045-0.050 mg/kg body weight per day by subcutaneous administration.
  Concomitant therapy with non-androgenic anabolic steroids in patients with Turner Syndrome can enhance the growth response.
- Growth failure in prepubertal children due to chronic renal failure (CRF):
  1.4 mg/m2 body surface area, approximately equal to 0.045-0.050 mg/kg body weight, per day by subcutaneous administration.
- Growth failure in short children born small for gestational age (SGA):
  The recommended daily dose is 0.035 mg/kg body weight (or 1 mg/m2/day, equal 0.1 IU/kg body weight/day or 3 IU/m2/day) per day, by subcutaneous administration.
  Treatment should be discontinued when the patient has reached a satisfactory adult height, or the epiphyses are fused.
  For growth disturbance in short children born SGA, treatment is usually recommended until final height is reached. Treatment should be discontinued after the first year if height velocity SDS is below +1. Treatment should be discontinued when final height is reached (defined as height velocity <2 cm/year), and if confirmation is required if bone age is >14 years (girls) or >16 years (boys), corresponding to closure of the epiphyseal growth plates.

Adults:

- Growth hormone deficiency in adults
  At the start of somatropin therapy, low doses of 0.15-0.3 mg are recommended, given as a daily subcutaneous injection. The dose should be adjusted stepwise, controlled by Insulin-like Growth Factor 1 (IGF-1) values. The recommended final GH dose seldom exceeds 1.0 mg/day. In general the lowest efficacious dose should be administered. In older or overweight patients, lower doses may be necessary.

For administration of the solution for injection of Saizen follow the instructions given in the package leaflet and in the instruction manual provided with the selected auto-injector: cool.click needle-free auto-injectors or easypod auto-injector.

Intended users of easypod are primarily children starting from the age of 7 up to adults. Use of the devices by children should always be made under adult's supervision.

For instructions for preparation please see section "Special precautions for disposal and other handling".

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Somatropin should not be used for growth promotion in children with closed epiphyses.

Somatropin should not be used in cases with active neoplasia or/and evidence of any progression or recurrence of an underlying intra-cranial lesion.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somatropin.

In children with chronic renal disease, treatment with somatropin should be discontinued at renal transplantation.

Since growth hormone deficiency may be an early sign of the presence of a pituitary tumour (or, rarely, other brain tumours), the presence of such tumours should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumour.

Special warnings and precautions for use

Treatment should be carried out under the regular guidance of a physician who is experienced in the diagnosis and management of patients with growth hormone deficiency. Do not exceed the maximum daily dose (Please see the Posology).

Patients with an intra or extracranial neoplasia in remission who are receiving treatment with growth hormone should be examined carefully and at regular intervals by the physician.

Patients with growth hormone deficiency secondary to an intracranial tumour should be examined frequently for progression or recurrence of the underlying disease process.

In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

Prader-Willi Syndrome

Somatropin is not indicated for the long-term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi Syndrome, unless they also have a diagnosis of growth hormone deficiency. There have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with Prader-Willi Syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

Leukaemia

Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Insulin sensitivity

Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin containing product therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy.

Stable background retinopathy should not lead to discontinuation of somatropin replacement therapy.

In case of development of preproliferative changes and the presence of proliferative retinopathy somatropin replacement therapy should be discontinued.

Thyroid function

Growth hormone increases the extra thyroid conversion of T4 to T3 and may, as such, unmask incipient hypothyroidism. In patients receiving replacement therapy with thyroxine mild hyperthyroidism may occurred. Thyroid function should be evaluated before starting Saizen® therapy and regularly assessed during treatment, not less frequently than annually. If hypothyroidism is diagnosed in the course of Saizen® therapy, it should be corrected. In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

Benign intracranial hypertension

Fundoscopic examination should be performed routinely before initiating treatment with Saizen® to exclude pre-existent papilloedema and repeated if there is any clinical suspicion (e.g. severe or recurrent headache, visual problems, nausea and/or vomiting). If papille oedema is confirmed by fundoscopy a diagnosis of benign intracranial hypertension (or pseudotumour cerebri) should be considered and Saizen treatment should be discontinued. At present there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary and treatment should be discontinued if intracranial hypertension recurs.

Pancreatitis

Although rare, pancreatitis should be considered in somatropin-treated patients, especially children who develop abdominal pain.

Antibodies

As with all somatropin containing products, a small percentage of patients may develop antibodies to somatropin. The binding capacity of these antibodies is low and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy.

Slipped capital femoral epiphysis is often associated with endocrine disorders such as growth hormone deficiency and hypothyroidism, and with growth spurts. In children treated with growth hormone, slipped capital femoral epiphysis may either be due to underlying endocrine disorders or to the increased growth velocity caused by the treatment. Growth spurts may increase the risk of joint-related problems, the hip joint being under particular strain during the prepubertal growth spurt. Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in children treated with Saizen.

Patients with growth failure due to chronic renal failure should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy and it is uncertain whether these problems are affected by growth hormone therapy. X-rays of the hip should be obtained prior to initiating therapy.

In children with chronic renal failure, renal function should have decreased to below 50% of normal before therapy is instituted. To verify the growth disturbance, growth should have been followed for a year before institution of therapy. Conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism and nutritional status for one year prior to the treatment) should have been established and should be maintained during treatment. Treatment should be discontinued at the time of renal transplantation.

In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment.

For SGA patients it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, increased body mass index, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.

For SGA patients it is recommended to measure IGF-I level before start of treatment and twice a year thereafter. If on repeated measurements IGF-I levels exceed +2 SD compared to references for age and pubertal status, the IGF-I/IGFBP-3 ratio could be taken into account to consider dose adjustment.

Experience in initiating treatment in SGA patients near onset of puberty is limited. It is therefore not recommended to initiate treatment near onset of puberty. Experience with SGA patients with Silver-Russel syndrome is limited.

Some of the height gain obtained with treating short children born SGA with somatropin may be lost if treatment is stopped before final height is reached.

Fluid retention is expected during growth hormone replacement therapy in adults.

In case of persistent oedema or severe paraesthesia the dosage should be decreased in order to avoid the development of carpal tunnel syndrome.

The injection site should be varied to prevent lipoatrophy.

Growth Hormone Deficiency in the Adult is a lifelong condition and should be treated accordingly, however experience with patients over sixty years and experience with prolonged treatment is limited.

In all patients developing acute critical illness, the possible benefit of treatment with somatropin must be weighed against the potential risk involved.

Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth hormone.

In addition, initiation of growth hormone replacement may unmask secondary adrenal insufficiency in some patients by reducing the activity of 11β-hydroxysteroid dehydrogenase, type 1 (11β-HSD1), an enzyme converting inactive cortisone to cortisol. Initiation of somatropin in patients receiving glucocorticoid replacement therapy may lead to manifestation of cortisol deficiency. Adjustment of glucocorticoid dose may be required. Because oral oestrogens may reduce the serum IGF-1 response to somatropin treatment, patients receiving oral oestrogen replacement may require greater somatropin dosages.

Data from an interaction study performed in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolized by cytochrome P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsivants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Pregnancy and lactation

Pregnancy:

From the reproductive studies performed in animals with somatropin containing products, there is no evidence of an increased risk of adverse reactions for the embryo or foetus. There are no data from the use of somatropin during pregnancy in animals. (See section Preclinical safety data). Therefore, somatropin containing products are not recommended during pregnancy and in woman of childbearing potential not using contraception.

Lactation:

There have been no clinical studies conducted with somatropin in breast-feeding women. It is not known whether somatropin is excreted in human milk. Therefore caution should be exercised when somatropin is administered to breast-feeding women.

Effects on ability to drive and use machines

Somatropin-containing products have no influence on the ability to drive and use machines.

Undesirable effects

Up to 10 % of patients may experience redness and itching at the site of injection, particularly when the subcutaneous route is used.

Fluid retention is expected during growth hormone replacement therapy in adults. Oedema, joint swelling, arthralgias, myalgias and paresthesias may be clinical manifestations of fluid retention. However, these symptoms / signs are usually transient and dose dependent.

Adult patients with growth hormone deficiency, following diagnosis of growth hormone deficiency in childhood, reported side-effects less frequently than those with adult onset growth hormone deficiency.

Antibodies to somatropin can form in some patients; the clinical significance of these antibodies is unknown, though to date the antibodies have been of low binding capacity and have not been associated with growth attenuation except in patients with gene deletions. In very rare instances, where short stature is due to deletion of the growth hormone gene complex, treatment with growth hormone may induce growth attenuating antibodies.

Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposing factors.

Pancreatitis has been reported in post-marketing studies during growth hormone therapy.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Very rare (<1/10,000)	Frequency unknown
Nervous system disorders	Headache (isolated), carpal tunnel syndrome (in adults)	Idiopathic intracranial hypertension (benign intracranial hypertension) Carpal tunnel syndrome (in children)		
Musculoskeletal and connective tissue disorders			Slipped capital femoral epiphysis (Epiphysiolysis capitis femoris), or avascular necrosis of the femoral head	
Immune system disorders				Localised and generalised hypersensitivity reactions
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders	In adults: Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paresthesia.	In children: Fluid retention: peripheral oedema, stiffness, arthralgia, myalgia, paresthesia.		Insulin resistance can result in hyperinsulinism and in rare cases in hyperglycemia.
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Injection site reactions: Localized lipoatrophy, which can be avoided by varying the site of injection			
Gastrointestinal disorders				Pancreatitis

Overdose

No cases of acute overdose have been reported. However, exceeding the recommended doses can cause side effects. Overdose can lead to hypoglycaemia and subsequently to hyperglycaemia. Moreover, somatropin overdose is likely to cause manifestations of fluid retention.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues, ATC code: H01AC01

Saizen contains recombinant human growth hormone produced by genetically engineered mammalian cells.

It is a peptide of 191 amino acids identical to human pituitary growth hormone with respect to amino acid sequence and composition as well as peptide map, isoelectric point, molecular weight, isomeric structure and bioactivity.

Growth hormone is synthesised in a transformed murine cell line that has been modified by the addition of the gene for pituitary growth hormone.

Saizen is an anabolic and anticatabolic agent which exerts effects not only on growth but also on body composition and metabolism. It interacts with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes and hematopoietic cells. Some, but not all of its effects are mediated through another class of hormones known as somatomedins (IGF-1 and IGF-2).

Depending on the dose, the administration of Saizen elicits a rise in IGF-1, IGFBP-3, non-esterified fatty acids and glycerol, a decrease in blood urea, and decreases in urinary nitrogen, sodium and potassium excretion. The duration of the increase in GH levels may play a role in determining the magnitude of the effects. A relative saturation of the effects of Saizen at high doses is probable. This is not the case for glycemia and urinary C-peptide excretion, which are significantly elevated after high doses (20 mg).

In a randomised clinical trial, three years treatment of pre-pubertal short children born SGA with a dose of 0.067 mg/kg/day resulted in a mean gain of +1.8 height-SDS. In those children who did not receive treatment beyond 3 years, part of the treatment benefit was lost, but the patients retained a significant gain of +0.7 height-SDS at final height ($p<0.01$ compared to baseline). Patients who received a second treatment course after a variable period of observation experienced a total gain of +1.3 height-SDS ($p=0.001$ compared to baseline) at final height. (The mean cumulative treatment duration in the latter group was 6.1 years). The gain in height-SDS (+1.3±1.1) at final height in this group was significantly ($p<0.05$) different from the gain in height-SDS obtained in the first group (+0.7±0.8) that received only 3.0 years of treatment on average.

A second clinical trial investigated two different dose regimens over four years. One group was treated with 0.067 mg/kg/day for 2 years and then observed without treatment for 2 years. The second group received 0.067 mg/kg/day in the first and third year and no treatment in the second and fourth year. Either treatment regimen resulted in a cumulative administered dose of 0.033 mg/kg/day over the four-year study period. Both groups showed a comparable acceleration of growth and a significant improvement of +1.55 ($p<0.0001$) and + 1.43 ($p<0.0001$) height-SDS respectively at the end of the four year study period. Long-term safety data are still limited.

Pharmacokinetic properties

The pharmacokinetics of Saizen are linear at least up to doses of 8 IU (2.67 mg). At higher doses (60 IU/20 mg) some degree of non-linearity cannot be ruled out, however with no clinical relevance.

Following intravenous administration in healthy volunteers the volume of distribution at steady-state is around 7 L, total metabolic clearance is around 15 L/h while the renal clearance is negligible, and the drug exhibits an elimination half-life of 20 to 35 min.

Following single-dose subcutaneous and intramuscular administration of Saizen, the apparent terminal half-life is much longer, around 2 to 4 hours. This is due to a rate limiting absorption process.

The absolute bioavailability of both routes is 70-90 %.

Maximum serum growth hormone (GH) concentrations are reached after approximately 4 hours and serum GH levels return to baseline within 24 hours, indicating that no accumulation of GH will occur during repeated administrations.

Saizen solutions for injection (5.83 and 8.00 mg/ml) administered subcutaneously have been shown to be bioequivalent versus the 8 mg freeze-dried formulation.

Preclinical safety data

The local tolerability of Saizen solution for injection was shown to be good and suitable for subcutaneous administration, when injected in animals at a concentration of 8.00 mg/ml and volumes of 1 ml/site.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. Formal carcinogenicity bioassays were not performed. This is justified, given the proteinous nature of the drug substance and the negative outcome of the genotoxicity testing. The potential effects of recombinant human growth hormone on the growth of pre-existing tumours have been evaluated through in vitro and in vivo experiments which have shown that recombinant human growth hormone is not expected to cause or stimulate tumours in patients. Reproductive toxicology studies do not indicate any adverse effect on fertility and reproduction, despite administration of doses sufficiently high to produce some pharmacological effects on growth.

Incompatibilities

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

Shelf life

24 months

Chemical physical and microbiological in use stability has been demonstrated for 28 days at 2 - 8°C, of which up to 7 consecutive days can be at max. 25°C.

Other in-use storage times and conditions are the responsibility of the user. After first injection, the Saizen cartridge or the easypod auto-injector containing the Saizen cartridge has to be stored in a refrigerator (2 - 8°C) for a maximum of 28 days, of which up to 7 consecutive days can be outside a refrigerator at max. 25°C. When stored outside of the refrigerator for up to 7 consecutive days, the Saizen cartridge must be returned to the refrigerator and used within 28 days after first injection. Do not freeze. Any remaining amounts should be discarded after 28 days.

Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package to protect from light.

When containing a cartridge of Saizen, the easypod auto-injector has to be stored in a refrigerator (2°C-8°C). When using the cool.click needle-free auto-injectors, only the cartridge of Saizen should be stored in a refrigerator (2°C-8°C).

Nature and contents of container

The container is a colourless type I glass cartridge with closure consisting of a bromobutyl rubber plunger stopper and an aluminium crimp cap with a bromobutyl rubber single inlay. Saizen 8 mg/ml solution for injection is available in the following pack sizes:

Pack of 1 cartridge, each containing 1.50 ml solution (12 mg somatropin).

Pack of 5 cartridges, each containing 1.50 ml solution (12 mg somatropin).

Pack of 1 cartridge, each containing 2.50 ml solution (20 mg somatropin).

Pack of 5 cartridges, each containing 2.50 ml solution (20 mg somatropin).

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

The cartridge containing the solution of Saizen 8 mg/ml is for use only with the cool.click needle-free auto-injectors or the easypod auto-injector.

For storage of auto-injectors containing a cartridge, see section "Special precautions for storage".

The solution for injection should be clear to slightly opalescent with no particles and without visible signs of deterioration. If the solution contains particles, it must not be injected.

Any unused product or waste material should be disposed of in accordance with local requirements.

Important information

For administration of Saizen, please read the following instructions carefully.

When the medicine is injected into the same place every time for a long time, it can cause damage. It is important to keep changing the place where you have your injection. Your doctor or pharmacist can speak to you about which part of the body you should use. Do not use any areas in which you feel lumps, firm knots, depressions, or pain; talk to your doctor or pharmacist about anything you find. Clean the skin at the injection site with soap and water.

The cartridge containing the solution of Saizen is ready to be used for administration with your cool.click needle-free auto-injectors or easypod auto-injector.

Place all elements needed for the injection of the solution on a clean surface and wash your hands with soap and water.

The solution should be clear to slightly opalescent with no particles and without visible signs of deterioration. If the solution contains particles, it must not be injected.

How to perform your daily self-administration of Saizen

For instructions on how to load the cartridge into the cool.click needle-free auto-injectors or easypod auto-injector and inject the solution of Saizen, please carefully read the corresponding instruction manual provided with each auto-injector. Intended users of easypod are primarily children starting from the age of 7 up to adults. Use of the devices by children should always be made under adult's supervision.

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