“澳洲”瑞樂沙旋達碟 衛署藥輸字第 025082 號

RELENZA ROTADISKS™ (Zanamivir 5mg) “Australia”

定性與定量組成

每一片 *RELENZA ROTADISK* 含有 4 個規則間隔的雙面錫箔泡囊，每一個泡囊中都含有由微粒化之 zanamivir (5 毫克)及乳糖(20 毫克)混合而成的白色至灰白色粉劑。

劑型

吸入用粉劑。

臨床特性

【適應症】

本藥須由醫師處方使用

治療流行性感冒

RELENZA 適用於治療及預防成人及兒童(≥ 5 歲)之 A 型及 B 型流行性感冒。

【劑量與用法】

RELENZA 僅可使用隨藥提供的碟型吸入器(*DISKHALER*™)以經口吸入的方式投入呼吸道。

對準備將其他吸入用藥(如速效性支氣管擴張劑)和 *RELENZA* 同時使用的患者，應建議其先使用該藥再使用 *RELENZA*。

- **成人**

治療流行性感冒

RELENZA 的建議劑量爲連續 5 天，每天兩次，每次吸入兩劑(2×5 毫克)，每天的總吸入劑量爲 20 毫克。

爲獲得最大效益，症狀出現後應盡快開始治療(最好在兩天之內)。

預防性治療

RELENZA 的建議劑量爲連續 10 天，每天一次吸入兩劑(2×5 毫克)，每天的總吸入劑量爲 10 毫克。如果接觸風險的時間超過 10 天，可將此療程延長，最多可延長至 1 個月。

應依處方完成整個預防性治療的療程。

- **兒童**

不須調整劑量(*參見藥物動力學*)。

- **老年人**

不須調整劑量(*參見藥物動力學*)。

- **腎功能損害者**

不須調整劑量(*參見藥物動力學*)。

- **肝功能損害者**

不須調整劑量(*參見藥物動力學*)。

【禁忌症】

對本製劑中之任何成分過敏者*(參見賦形劑)*。

【警語及注意事項】

感染流行性感冒可能會使氣道的過敏反應性升高。在因流行性感冒而接受治療的患者中，曾有在使用 zanamivir 後出現支氣管痙攣及(或)呼吸功能降低之現象的報告，但極爲罕見，其中部份病患過去並無任何呼吸道疾病病史。任何出現此類反應的病患都應停用 zanamivir，並就醫檢查。併有呼吸道疾病的患者在使用 zanamivir 時，應隨時備妥速效性支氣管擴張劑*(參見劑量與用法)*。

類似過敏反應，包括口咽部水腫、嚴重皮膚疹，曾在 ***RELENZA*** 上市後使用經驗中報告過。若發生過敏反應或懷疑是過敏反應，應停用 ***RELENZA*** 並給予適當處置。

雖然流行性感冒也可能引起神經系統與行爲方面的症狀；但許多上市後報告(大部分來自日本及兒童受試者)提到流行性感冒患者在接受包含 ***RELENZA*** 在內的神經胺酸酶抑制劑(neuraminidase inhibitor)治療時，有癲癇、譫妄、幻覺與異常行爲等表現。這些症狀主要發生於疾病初期，往往突然出現之後又迅速消退。目前尚未證實 ***RELENZA*** 與這些症狀的關聯性。如果出現神經精神方面的症狀，應個別評估每位患者繼續接受治療的風險與效益。

【藥物交互作用】

Zanamivir 並不會和蛋白質結合，也不會在肝臟代謝或改變結構。不太可能會發生具臨床意義的藥物交互作用。

【懷孕與授乳】

於妊娠期間使用 ***RELENZA*** 的安全性尚未獲得確立。

針對大鼠(rat)與兔子所進行的生殖研究顯示，zanamivir 會透過胎盤轉移。在針對大鼠所進行的研究中，並未發現任何證據顯示投予 zanamivir 會造成畸形、生殖力損害、或是對子代的出生前發育或出生後發育造成具臨床意義的損害。不過，目前並無任何關於 zanamivir 是否會透過人類胎盤轉移的資料。

懷孕期間不可使用 ***RELENZA***，尤其是在第一孕期(妊娠的最初三個月)，除非醫師認爲其對患者的潛在效益超越胎兒可能面臨的任何風險。

大鼠的研究顯示，zanamivir 會分泌進入乳汁。不過，目前並無任何關於 zanamivir 是否會分泌進入人類乳汁的資料。

由於經驗有限，因此，只有在醫師認爲其對授乳母親之潛在效益超越嬰兒可能面臨之任何風險的情況下，才可考慮對授乳母親使用 ***RELENZA***。

【對駕駛及機械操作能力的影響】

無任何已知影響。

【不良反應】

本品尚未證明用於有潛在高風險病人的療效及安全性。也沒有在足以認定病況嚴重或不穩定而即將需要住院的病人，使用本品治療流行性感冒的資料。

臨床試驗資料

RELENZA 經口吸入投予後的耐受性極佳。在臨床試驗中，包括那些針對高危險患者(老年人，以及併有某些慢性疾病的患者)所進行的研究，*RELENZA* 組中所發生的不良反應都和安慰劑組相當。

上市後的資料

極常見	≥1/10
常　見	≥ 1/100 但<1/10
不常見	≥ 1/1000 但<1/100
罕　見	≥ 1/10,000 但<1/1000
極罕見	<1/10,000

RELENZA 被核准用於治療流行性感冒之後曾發生下列事件。

免疫系統疾患：

極罕見：　過敏性反應，包括顏面水腫及口咽水腫

呼吸道、胸部及縱膈疾患：

極罕見：　支氣管痙攣、呼吸困難

皮膚及皮下組織疾患：

極罕見：　皮疹、蕁麻疹

極罕見：　嚴重皮膚反應，包括多形性紅斑、史蒂芬強生症候群(Stevens-Johnson syndrome)及毒性表皮壞死溶解症

【過量】

由於本品有物理及投予途徑上的限制，而且 zanamivir 的口服生體可用率很差(2 至 3%)，因此不太可能發生意外過量的問題。曾以經口吸入的方式投予劑量最高達 64 mg/day (約爲每日最高建議劑量的 3 倍)的 zanamivir，結果並未發生不良反應。此外，也曾連續 5 天以靜脈注射的方式全身性投予最高達 1200 mg/day 的劑量，結果也未發生任何不良反應。

藥理學特性

【藥效學】

ATC 代碼：J05AH01。

Zanamivir 是一種強效且具高度選擇性神經胺酸酶(neuraminidase；流行性感冒病毒表面酵素)抑制劑。病毒的神經胺酸酶可幫助新形成的病毒粒子自被感染的細胞中釋放出來，也會使病毒更容易通過黏膜抵達上皮細胞表面，從而使病毒得以感染其

它細胞。體外及體內試驗都顯示，抑制此酵素可遏阻 A 型及 B 型流行性感冒病毒的複製，此抑制作用並可涵蓋 A 型流行性感冒病毒的所有已知神經胺酸酶亞型。Zanamivir 係於細胞外部產生作用。它可抑制感染性流行性感冒病毒粒子自呼吸道上皮細胞釋出，從而降低 A 型與 B 型流行性感冒病毒的繁殖速度。流行性感冒病毒的複製作用僅局限於呼吸道的表面上皮。將 zanamivir 局部投予於此部位的療效已在臨床研究中獲得證實。臨床試驗資料顯示，和安慰劑相比較，使用 zanamivir 治療急性流行性感冒感染可降低病毒自呼吸道釋出的作用，而且至今均尚未偵測到對 zanamivir 之感受性降低的病毒的出現。

【藥物動力學】

【吸收】

人體藥物動力學研究的結果顯示，此藥物的絕對口服生體可用率極低(平均爲 2%)。針對經口吸入之 zanamivir 所進行的類似研究顯示，約有 10 至 20%的劑量會被吸收進入體內，且通常可於 1 至 2 小時內達到最高血中濃度。由於此藥物的吸收不佳，所達到的全身濃度也極低，因此在經口吸入之後，並不會出現任何有意義的 zanamivir 全身曝藥量。目前並無任何證據顯示重覆經口吸入投藥後的動力學概況會有所改變。

【分佈】

經口吸入投藥後，zanamivir 會以極高的濃度廣泛地沉積在整個呼吸道中，從而將藥物遞送到流行性感冒的感染部位。曾於投予單劑 10 毫克的劑量後檢測氣道上皮層(流行性感冒病毒進行複製的主要部位)的 zanamivir 濃度。投藥後 12 小時及 24 小時所測得的 zanamivir 濃度分別要抑制 50%比病毒神經胺酸酶之所需濃度(IC_{50})的中位數值高出約 340 倍及 52 倍。呼吸道中的高濃度 zanamivir 會迅速對病毒的神經胺酸酶產生抑制作用。主要的兩個藥物沉積部位爲口咽及肺部(平均值分別爲 77.6%及 13.2%)。

【代謝】

Zanamivir 已證實會以原型藥物的型式經由腎臟排泄，並且不會經過任何代謝。

【排除】

Zanamivir 經口吸入投予後的血清半衰期爲 2.6 至 5.05 小時。它會以原型藥物的型式完全排入尿液中。依尿液廓清率估算，其整體廓清率爲 2.5 至 10.9 l/h。其腎臟排除作用可於 24 小時內完成。

【特殊病患族群】

- 小兒病患：

一項開放性單一劑量研究曾針對 24 名 3 個月至 12 歲大的小兒病患評估噴霧吸入劑型(10 毫克)與乾粉吸入劑型(10 毫克)之 zanamivir 的藥物動力學。兒童的全身曝藥量和使用 10 毫克吸入用粉劑的成人大致相當。

- **高齡病患：**

在每日 20 毫克的治療劑量下，其生體可用率極低(10 至 20%)，因此患者並不會出現任何有意義的 zanamivir 全身曝藥量。藥物動力學隨年齡而發生令任何改變皆不太可能具有臨床上的重要性，因此並不建議調整劑量。

- **腎功能損害患者：**

在每日 20 毫克的治療劑量下，其生體可用率極低(10 至 20%)，因此患者並不會出現任何有意義的 zanamivir 全身曝藥量。由於 zanamivir 的安全範圍極廣，嚴重腎衰竭患者雖然可能出現曝藥量升高的現象，但一般並不認爲會造成問題，也不須調整劑量。

- **肝功能損害患者：**

Zanamivir 在人體內並不會代謝，因此，對肝功能損害患者並不須調整劑量。

【臨床研究】

當依照建議用於治療健康或高危險群患者的流行性感冒時，zanamivir 不僅可減輕症狀，亦可使病期縮短。一項針對主要第 III 期治療研究(NAIB3001、NAIA3002、NAIB3002 及 NAI30008)所進行的綜合分析顯示，在使用 zanamivir 的患者中，流行性感冒症狀獲得緩解的中位時間可較使用安慰劑者縮短 1.5 天(p 值小於 0.001)。在使用安慰劑的患者中，併發症的發生率爲 208/711 (29%)，在使用 zanamivir 的患者中則降低至 171/769 (22%) (相對風險：0.77；95% CI：0.65 至 0.92；p=0.004)。在使用安慰劑的患者中，使用抗生素治療併發症的比例爲 136/711 (19%)，在使用 zanamivir 的患者中則降低至 110/769 (14%) (相對風險：0.76；95% CI：0.60 至 0.95；p=0.021)。

研究顯示，如果在症狀出現後盡快開始治療，zanamivir 可發揮最佳的療效。

使用 zanamivir 進行預防性治療已證實可有效預防成人與兒童(5 歲[含]以上)感染流行性感冒。從出現症狀且經實驗室確認的流行性感冒來看，在流行性感冒預防性治療的建議劑量下，和安慰劑相比較，zanamivir 可提供 67 至 79%的保護效果，和活性對照藥物相比較，亦可提供 56 至 61%的保護效果。

【臨床前安全性資料】

在動物毒性研究中，投予 zanamavir 並不會引發任何臨床相關影響。Zanamivir 並不具基因毒性，在針對大鼠及小鼠所進行的長期致癌性研究中，也未發現任何顯示其具有致癌性的證據。

藥劑學特性

【賦形劑】

乳糖(含乳蛋白)。

【不相容性】

無任何已知的不相容性。

【有效期限】

有效期限標示於包裝上。

【貯存注意事項】

RELENZA ROTADISKS 不可貯存於溫度超過 30℃以上的處所。

【容器之性質與內容物】

RELENZA ROTADISKS 爲一含有 4 個規則分佈之泡囊的環型錫箔碟片(旋達碟)，每一個泡囊中都含有 5 毫克的 zanamivir 及 20 毫克的乳糖。包裝外盒中附有一個用以投藥的碟型吸入器(*DISKHALER*)。

【使用及操作說明】

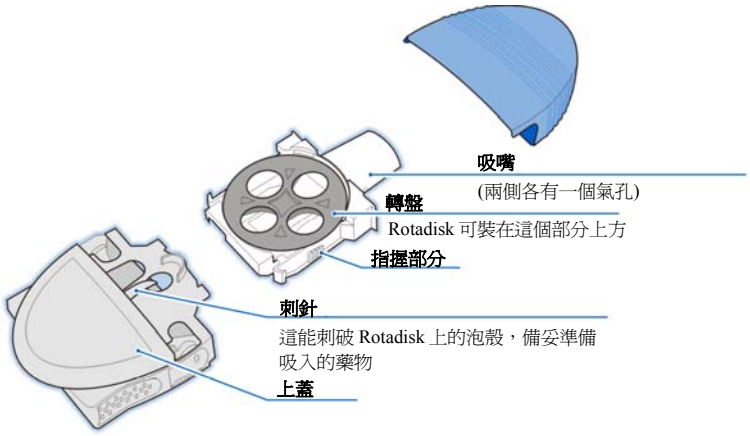
此粉末製劑須經口吸入至肺臟。碟型吸入器(*DISKHALER*)中裝有一片碟片，藥物即盛裝於此碟片的各個泡囊中，這些泡囊會在操作吸入器的過程中打開。

病患須知說明書使用指示：

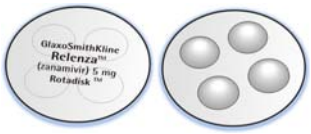
初次使用前，請先仔細閱讀使用步驟教學。如果您對 *DISKHALER* 的使用方式仍有疑問，請要求藥師爲您完整解說一遍。

***DISKHALER* 可分爲三個部分：**

在您研讀使用步驟教學前，切勿拆開這項裝置。



***ROTADISK* 可裝進 *DISKHALER* 內**



ROTADISK 可裝在 *DISKHALER* 的轉盤上方。

ROTADISK 的四個泡殼內均含有 *RELENZA* 的單次劑量。

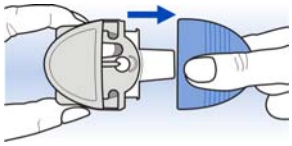
重要：

- 在將 *ROTADISK* 裝上 *DISKHALER* 前，不可刺破任何一個泡殼。
- 未使用時可將 *ROTADISK* 留在 *DISKHALER* 上；不過，請等到準備吸入藥物前再刺破泡殼。
- 請保持 *DISKHALER* 的清潔。使用後請以紙巾擦拭吸嘴，並在未使用時將藍色外蓋裝回原位。

使用步驟教學：如何使用您的*RELENZA DISKHALER*

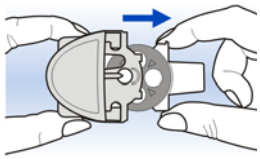
將*ROTADISK*裝入*DISKHALER*：

1. **移除藍色外蓋。**

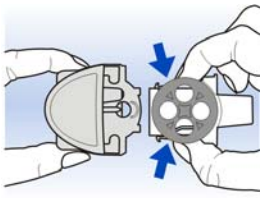


檢查吸嘴內外是否清潔。

2. **如圖所示抓住滑盤向外拉出，直到停下為止。**

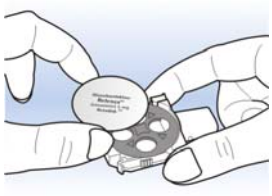


3. **輕壓白色滑盤兩側的指握部分。**
將滑盤從裝置主體取出。



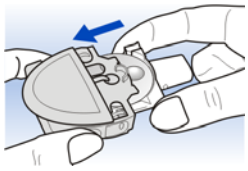
白色滑盤應可輕易取出。

4. **將一組新的 *RELENZA ROTADISK* 放上轉盤。**



確認印刷面在上，泡殼朝下。
將泡殼裝進轉盤的圓孔。

5. **將白色滑盤推回裝置主體內部。**

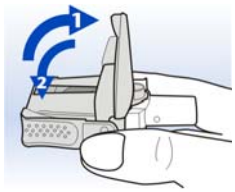


若您尚未準備立即吸入 *RELENZA* 藥物，請將藍色外蓋裝回原位。

準備您要吸入的藥物：

請等到準備吸入藥物前，再操作以下步驟。

6. **將 *DISKHALER* 固定於水平狀態。**



使 *DISKHALER* 保持在水平狀態。

盡量掀開上蓋。
上蓋必須完全垂直，以確保能徹底刺破泡殼。

將上蓋推回原位。
現在您的 DISKHALER 已備妥可供使用。在吸入藥物前，請保持裝置水平。

吸入藥物：

7. 請您暫時還不要將 *DISKHALER* 放入口中。將 *DISKHALER* 從您的嘴邊移開，在舒適範圍內盡可能地吐氣。請不要對著 *DISKHALER* 吹氣，這樣會將藥物粉末吹出 *ROTADISK*。

 使 *DISKHALER* 保持在水平狀態。

將吸嘴置入齒間，緊閉雙唇包住吸嘴；

請勿啃咬吸嘴。不要阻塞吸嘴側邊的氣孔。

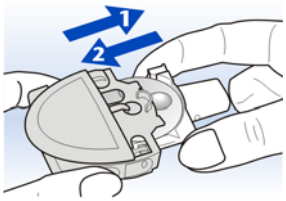
從吸嘴快速地深吸一口氣；然後憋住這口氣約幾秒鐘。

將 *DISKHALER* 從口中移開。

繼續屏息幾秒鐘，或在舒適範圍內盡可能延長這段時間。

準備下個泡殼(劑量的第二部分)：

8. 盡量向外拉出白色滑盤(請勿將其完全取出)，然後將它推回原位。



這個動作會轉動轉盤，使下個泡殼出現。

必要時重複這個動作，直到完整的泡殼出現在刺針下方。

重複步驟 6 與步驟 7 以吸入藥物。

9. 在您吸入完整劑量的藥物後(通常爲兩個泡殼)：

請以紙巾擦拭吸嘴，並將藍色外蓋裝回原位。務必保持 *DISKHALER* 的清潔。

更換*ROTADISK*：

10. 當四個泡殼全都用完時，從 *DISKHALER* 取下 *ROTADISK*，然後按照步驟 1 至 5 裝上一組新的藥物。

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RELENZA™

Zanamivir

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each *RELENZA ROTADISK*™ consists of four regularly spaced double foil blisters each containing a white to off-white micronised powder mixture of zanamivir (5 mg) and lactose (20 mg).

PHARMACEUTICAL FORM

Inhalation powder.

CLINICAL PARTICULARS

Indications

Treatment of Influenza: *RELENZA* is indicated for treatment of both influenza A and B in adults and children (≥ 5 years).

Prophylaxis: *RELENZA* is indicated for prophylaxis of both influenza A and B in adults and children (≥ 5 years).

Dosage and Administration

RELENZA is for administration to the respiratory tract by oral inhalation only, using the *DISKHALER*™ device provided.

Patients scheduled to take inhaled drugs, e.g. fast acting bronchodilators, at the same time as *RELENZA* should be advised to administer that drug prior to administration of *RELENZA*.

- **Adults**

Treatment of Influenza

The recommended dose of *RELENZA* is two inhalations (2 x 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg.

For maximum benefit, treatment should begin as soon as possible (preferably within two days) after onset of symptoms.

Prophylaxis

The recommended dose of *RELENZA* is two inhalations (2 x 5 mg) once daily for 10 days, providing a total daily inhaled dose of 10mg. This may be increased up to one month if the period of exposure risk extends beyond 10 days.

The full course of prophylaxis therapy should be completed as prescribed.

- **Children**

No dose modification is required (*see Pharmacokinetics*).

- **Elderly**

No dose modification is required (*see Pharmacokinetics*).

- **Renal impairment**

No dose modification is required (*see Pharmacokinetics*).

- **Hepatic impairment**

No dose modification is required (*see Pharmacokinetics*).

Contraindications

Hypersensitivity to any ingredient of the preparation (*see Pharmaceutical Particulars – List of Excipients*).

Warnings and Precautions

Influenza infection can be associated with increased airways hyper-responsiveness. There have been very rare reports of patients being treated for influenza who have experienced bronchospasm and/or decline in respiratory function after the use of *RELENZA*, some of whom did not have any previous history of respiratory disease. Any such patients should discontinue *RELENZA* and seek medical evaluation. Patients with underlying respiratory disease should have a fast acting bronchodilator available when taking *RELENZA* (*see Dosage and Administration*).

Allergic-like reactions, including oropharyngeal edema, serious skin rashes have been reported in postmarketing experience with *RELENZA*. *RELENZA* should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

Influenza can be associated with a variety of neurological and behavioural symptoms. There have been postmarketing reports (mostly from Japan and in paediatric subjects) of seizures, delirium, hallucination and abnormal behaviour in patients with influenza who were receiving neuraminidase inhibitors, including *RELENZA*. The events were observed mainly early in the illness and often had an abrupt onset and rapid resolution. The

contribution of *RELENZA* to these events has not been established. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Interactions

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely.

Pregnancy and Lactation

The safe use of *RELENZA* during pregnancy has not been established.

Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer in humans.

RELENZA should not be used in pregnancy, especially during the first trimester, unless the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

In rats zanamivir has been shown to be secreted into milk. However, there is no information on secretion into breast milk in humans.

As experience is limited, the use of *RELENZA* in nursing mothers should be considered only if the possible benefit to the mother is thought to outweigh any possible risk to the infant.

Effects on Ability to Drive and Use Machines

None known.

Adverse Reactions

Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

Clinical trial data

RELENZA is well tolerated by the oral inhaled route of administration. In clinical studies, including those studies with high risk patients (the elderly, and patients with certain chronic medical conditions), the adverse events reported were similar in the *RELENZA* and placebo groups.

Post-marketing data

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10,000 and <1/1000
Very rare	<1/10,000

The following events have been identified during post-approval use of *RELENZA* for the treatment of influenza.

Immune Systems Disorders

Very rare: Allergic-type reaction, including facial and oropharyngeal oedema.

Respiratory, thoracic and mediastinal disorders

Very rare: Bronchospasm, dyspnoea.

Skin and subcutaneous tissue disorders

Very rare: Rash, urticaria.

Very rare: Severe skin reactions including Erythema Multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis

Overdose

Accidental overdose is unlikely due to the physical limitations of the presentation, the route of administration and the poor oral bioavailability (2 to 3%) of zanamivir. Doses of zanamivir up to 64 mg/day (approximately 3 times the maximum daily recommended dose) have been administered by oral inhalation (by nebuliser) without adverse effects. Additionally, systemic exposure by intravenous administration of up to 1200 mg/day for five days showed no adverse effect.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code: J05AH01.

Zanamivir is a potent and highly selective inhibitor of neuraminidase, the influenza virus surface enzyme. Viral neuraminidase aids the release of newly formed virus particles from infected cells, and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. The inhibition of this enzyme is reflected

in both *in vitro* and *in vivo* activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication is confined to the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. Clinical trial data have shown that treatment of acute influenza infections with *RELENZA* produces reductions in virus shedding from the respiratory tract compared to placebo without any detectable emergence of virus with reduced susceptibility to zanamivir.

Pharmacokinetics

Absorption

Pharmacokinetic studies in humans have shown that the absolute oral bioavailability of the drug is low (mean 2%). Similar studies of orally inhaled zanamivir indicate that approximately 10 to 20% of the dose is systemically absorbed, with serum concentrations generally peaking within 1-2 hours. The poor absorption of the drug results in low systemic concentrations and therefore there is no significant systemic exposure to zanamivir after oral inhalation. There is no evidence of modification in the kinetics after repeated dosing with oral inhaled administration.

Distribution

After oral inhalation, zanamivir is widely deposited at high concentrations throughout the respiratory tract, thus delivering the drug to the site of influenza infection. Following a single 10 mg dose the concentrations of zanamivir were measured at the epithelial layer of the airways, the major sites of influenza viral replication. Zanamivir concentrations of approximately 340 and 52 fold above the median viral neuraminidase IC_{50} were measured at 12h and 24h, respectively. The high concentrations of zanamivir in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase. The two major sites of deposition are the oropharynx and the lungs (mean 77.6% and 13.2%, respectively).

Metabolism

Zanamivir has been shown to be renally excreted as unchanged drug, and does not undergo metabolism.

Elimination

The serum half-life of zanamivir following administration by oral inhalation ranges from 2.6 to 5.05 hours. It is entirely excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 l/h as approximated by urinary clearance. Renal elimination is completed within 24 hours.

Special Patient Populations

- **Children**

In an open-label single-dose study the pharmacokinetics of zanamivir have been evaluated in 24 paediatric subjects ages 3 months to 12 years using nebulised (10 mg) and dry powder (10 mg) inhalation formulations. The systemic exposure in children was similar to 10 mg of inhaled powder in adults.

- **Elderly**

At the therapeutic daily dose of 20 mg, bioavailabilty is low (10 to 20%), and as a result there is no significant systemic exposure of patients to zanamivir. Any alteration of pharmacokinetics that may occur with age is unlikely to be of clinical consequence and no dose modification is recommended.

- **Renal Impairment**

At the therapeutic daily dose of 20 mg, bioavailabilty is low (10 to 20%), and as a result there is no significant systemic exposure of patients to zanamivir. Given the wide safety margin of zanamivir the possible increased exposure in patients with severe renal failure is not considered problematic and no dose adjustment is required.

- **Hepatic Impairment**

Zanamivir is not metabolised, therefore dose adjustment in patients with hepatic impairment is not required.

Clinical Studies

RELENZA, when taken as recommended for treatment of influenza in otherwise healthy and high risk patients, alleviates the symptoms and reduces their duration. In a pooled analysis of the principle phase III treatment studies (NAIB3001, NAIA3002, NAIB3002 and NAI30008) the median time to alleviation of influenza symptoms was reduced by 1.5 days for patients taking *RELENZA* as compared to placebo ($p<0.001$). Complications were reduced from 208/711 (29%) of placebo patients to 171/769 (22%) of *RELENZA* patients (relative risk: 0.77; 95% CI: 0.65 to 0.92; $p=0.004$). Use of antibiotics for treatment of complications was reduced from 136/711 (19%) of placebo patients to 110/769 (14%) of *RELENZA* patients (relative risk: 0.76; 95% CI: 0.60 to 0.95; $p=0.021$).

The efficacy of *RELENZA* has been shown to be optimal if treatment is initiated as soon as possible after the onset of symptoms.

RELENZA given as prophylaxis has been shown to prevent influenza in adults and children (≥5 years). *RELENZA* given at the recommended dose for the prophylaxis of influenza provided 67-79% protection compared to placebo, and 56-61% protection compared to an active comparator against symptomatic, laboratory-confirmed influenza.

Pre-clinical Safety Data

Administration of zanamivir in animal toxicity studies was not associated with any clinically relevant effects. Zanamivir was not genotoxic and showed no evidence of carcinogenic potential in long term carcinogenicity studies in rats and mice.

PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose (which contains milk protein).

Incompatibilities

None known

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

RELENZA ROTADISKS should not be stored above 30°C.

Nature and Contents of Container

RELENZA ROTADISKS consist of a circular foil disk (a Rotadisk) with four regularly distributed blisters each containing 5 mg of zanamivir and 20 mg of lactose. A *DISKHALER* is provided to administer the medication.

Instructions for Use/Handling

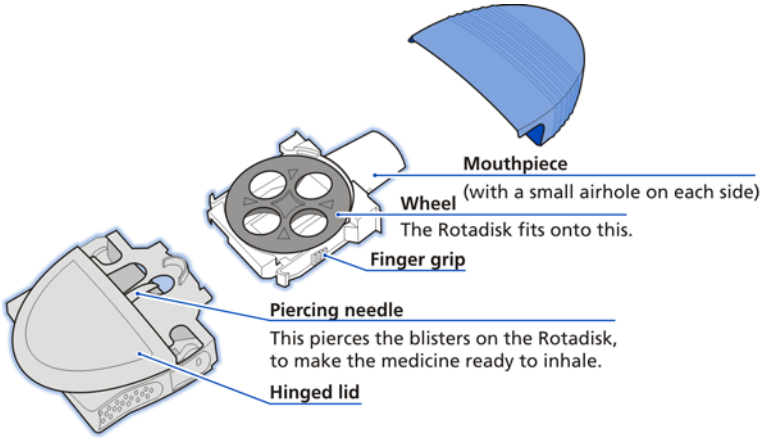
The powdered medicine is inhaled through the mouth into the lungs. The *DISKHALER* device is loaded with a disk which contains the medicine in individual blisters which are opened as the device is manipulated.

Instructions for the Patient Information Leaflet:

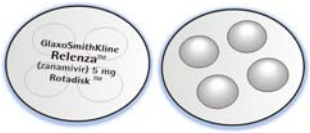
Read the step-by-step guide carefully before you use your first dose. If you're still not sure how to use the *DISKHALER*, ask you pharmacist to go through the instructions with you.

The *DISKHALER* has three parts:

Don't take it apart until you have looked at the step-by-step guide.



The *ROTADISK* fits into the *DISKHALER*



The *ROTADISK* fits onto the wheel of the *DISKHALER*.

Each of the four blisters on the *ROTADISK* contains a single dose of *RELENZA*.

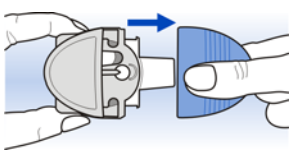
Important:

- Don’t pierce any of the blisters on the *ROTADISK* before you load it onto the *DISKHALER*.
- You can keep a *ROTADISK* on the *DISKHALER* between doses, but don’t pierce a blister until just before you inhale your dose.
- Keep the *DISKHALER* clean. Wipe the mouthpiece with a tissue after you use it, and replace the blue cover between uses.

STEP-BY-STEP GUIDE TO USING YOUR *RELENZA DISKHALER*

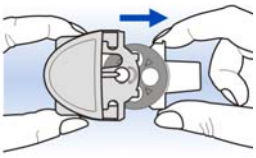
To load a *ROTADISK* into the *DISKHALER*:

1. Remove the blue cover.

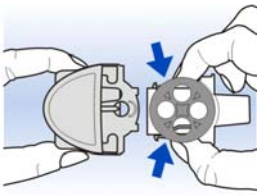


Check that the mouthpiece is clean, inside and outside.

2. Hold the white sliding tray as shown and pull it out until it stops.

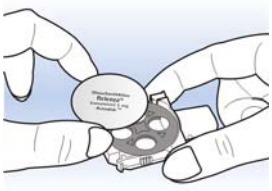


3. Gently squeeze the finger grips on the sides of the white tray. Remove the tray from the main body.



The white tray should come out easily.

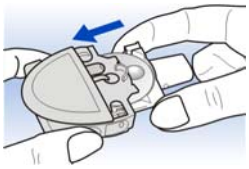
4. Place a new *RELENZA ROTADISK* on the wheel.



Make sure the printed side is up, with the blisters facing downwards.

The blisters fit into the holes in the wheel.

5. Push the white tray back into the main body.

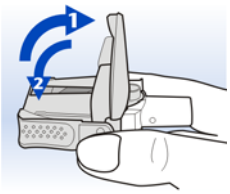


If you're not ready to inhale a dose of *RELENZA* straight away, replace the blue cover.

To get your dose ready to inhale:

Don’t do this until just before you inhale a dose.

6. Hold the *DISKHALER* horizontally.



Keep the *DISKHALER* horizontal

Flip the lid up as far as it will go.

The lid must be fully vertical, to make sure that the blister is pierced completely.

Push the lid back down.

Your DISKHALER is now ready for use. Keep it horizontal until you have inhaled your dose.

To inhale the medication:

7 Don’t put the *DISKHALER* into your mouth yet. Breathe out as far as is comfortable, keeping the *DISKHALER* away from your mouth. Don’t blow into the *DISKHALER*. If you do, you’ll blow the powder out of the *ROTADISK*.


Keep the *DISKHALER* horizontal

Place the mouthpiece between your teeth. Close your lips firmly around the mouthpiece.

Don’t bite the mouthpiece. Don’t block the airholes on the side of the mouthpiece.

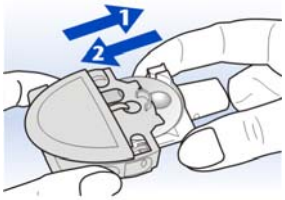
Take one quick, deep breath in through the mouthpiece. Hold this breath for a few seconds.

Remove the *DISKHALER* from your mouth.

Carry on holding your breath for a few more seconds or as long as is comfortable.

To prepare the next blister (the second part of your dose):

8. Pull the white tray out as far as it will go (don't remove it completely), then push it back in again.



This will turn the wheel so the next blister will appear.

Repeat if necessary until a full blister is positioned under the piercing needle.

Repeat steps 6 and 7 to inhale the medicine.

9. After you've inhaled the full dose (normally two blisters):

Wipe the mouthpiece with a tissue and replace the blue cover. It's important to keep the *DISKHALER* clean.

To replace the *ROTADISK*:

10. When all four blisters are empty, remove the *ROTADISK* from the *DISKHALER* and insert a new one, using steps 1 to 5.

Not all presentations are available in every country.

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