備勞喘® 100 微公克定量噴霧液
Berotec N 100 mcg/puff Metered Aerosol

衛署藥輸字第 023074 號

成分

每一噴霧劑量含

1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol hydrobromide (= fenoterol hydrobromide) 100 mcg

性質

以罹患氣喘及 COPD 之成年人與罹患氣喘兒童為對象，長達三個月之治療試驗顯示，BEROTEC 含 HFA 處方和含 CFC 處方具有治療相等性。

Fenoterol hydrobromide 是一直接作用的擬交感神經藥物，在治療劑量下會選擇性的刺激β_2受體，較高劑量下才會刺激β_1受體，與β_2受體結合後刺激 Gs-蛋白，活化腺　吟環狀　(adenyl cyclase)，增加 cAMP 活化蛋白激　A (protein kinase A)，使平滑肌細胞中的蛋白質磷酸化，依次促使 myosin light chain 激　磷酸化，抑制 phosphoinositide 水解，而開啟大傳導性，鈣離子活化之鉀離子通道(large-conductance calcium – activated potassium channels)，有些證據證實鉀離子通道(Maxi-K channel)可直接被 Gs-蛋白活化。

Fenoterol 鬆弛支氣管和血管平滑肌，可對抗支氣管收縮之刺激，如：組織胺、methacholine、冷空氣及過敏原(早期反應)。緊急給藥後，可抑制肥大細胞(mast cells)釋出支氣管收縮媒介物質及發炎之前驅介質(pro-inflammatory mediators)，已證實在使用高劑量的 fenoterol 後，可增加黏膜纖毛的清除效果。

口服及靜脈注射後具較高的血中濃度，可抑制子宮收縮，同時在較高劑量下觀察到下列新陳代謝現象：脂質分解、糖分解、高血糖和低血鉀症。低血鉀症主要因骨骼肌對鉀離子之吸收增加而引起。Fenoterol 興奮心臟β_2受體，增加心跳速率與心收縮力；在高於治療劑量時，並有β_1受體興奮性之作用。β致效劑常見震顫反應，不同於對支氣管平滑肌的作用，β致效劑之全身性作用會產生耐藥性。

臨床研究顯示 fenoterol 治療支氣管痙攣極有效，可預防運動、冷空氣和過敏原接觸早期反應引起之支氣管收縮。

藥物動力學

BEROTEC 的治療效果來自於藥物在呼吸道的局部作用，因此 BEROTEC 使支氣管擴張的藥效學與製劑中主成分之藥動學沒有關聯，藥動學的試驗

已顯示，含 HFA 處方與傳統含 CFC 處方之療效相當。
阻塞性肺疾病患者吸入 fenoterol hydrobromide 後數分鐘內即可產生支氣管擴張作用，且作用可持續 3 – 5 小時。
Fenoterol 吸入後，依吸入方法與吸入裝置不同而有差異，大約 10 – 30%的主成分會由定量噴霧劑釋出到達下呼吸道，剩餘部份則留在上呼吸道及口中，因此，部份經吸入投與的 fenoterol 會進入胃腸道，已知吸入一個噴霧劑量之 BEROTEC 100 微公克定量噴霧液之吸收率為劑量的 17%。吸收為雙相的，其中 30%的 fenoterol hydrobromide 迅速被吸收，半衰期為 11 分鐘，而緩慢吸收的 70%，其半衰期為 120 分鐘。
藥物之血中濃度與藥效時間效能曲線並無相關性，靜脈注射後全身的血漿濃度無法說明藥品吸入後之長效支氣管擴張作用。口服後約 60%的 fenoterol hydrobromide 被吸收，被吸收之藥物經由首渡代謝後，其口服之生體可用率降為 1.5%，這就是為什麼吸入後被吞入的主成分並不會增加全身性之血中濃度。
Fenoterol hydrobromide 全身性投與後，是經由三室模式進行排除($t_{1/2}\alpha$ = 0.42 分鐘，$t_{1/2}\beta$ = 14.3 分鐘，$t_{1/2}\gamma$ = 3.2 小時)。Fenoterol hydrobromide 在人體幾乎都是經由硫酸化進行代謝轉換，主要是在小腸壁進行。
Fenoterol hydrobromide 的原型藥物可穿透胎盤且會進入母乳中。
Fenoterol hydrobromide 在糖尿病患者之代謝狀態及效能資料尚不充足。

適應症

下列支氣管痙攣疾患之預防和治療，支氣管氣喘、阻塞性支氣管炎、慢性支氣管炎、氣腫以及伴隨支氣管痙攣之肺支氣管障礙。

用法用量

用量

a)急性氣喘發作

對大多數的患者，一個定量即可緩解症狀，若吸入 5 分鐘後呼吸沒有明顯的改善，可投與第二個劑量。

投與第二個劑量後，若治療仍未改善，可能需要再投與數個劑量，此時應立即請教醫師或就近送醫。

b) 預防運動引發的氣喘

每次 1 – 2 個定劑量，每天不得超過 8 個定劑量。

c)支氣管性氣喘及其他可逆性呼吸道狹窄的情況

若需要重複投與，每次 1 – 2 個定劑量，但每天不得超過 8 個劑量。

小孩必須在醫師指示及成人監護下，才可使用 BEROTEC 100 微公克定量噴霧液。

用法

為了成功的治療，應正確操作定量噴霧液裝置。
該裝置在最初使用之前，下壓活塞 2 次。

每次使用應注意以下規則：

1.移去護蓋。

2.深深呼氣。

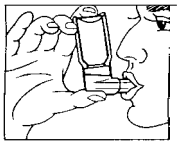

圖 1.

3.如圖 1.所示拿住定量噴霧液，並以雙唇啣口含器，箭頭和容器底部應朝上。

4.盡可能深深地吸氣，同時按壓容器的底部以釋出一個定劑量，停止呼吸數秒鐘，然後自口中移去口含器後呼氣。

5.使用後蓋上護蓋。

容器不透明，因此無法看出內容物何時被用完。此噴霧液可提供 200 個劑量，當 200 個劑量都被使用後，可能仍有少量液體留存，此時不能提供正確的治療劑量，請勿再使用。

噴霧器中的治療含量，可依下列方法檢查：

移去噴霧液劑之塑膠口含器，把噴霧液劑置於裝有水的容器中，觀察其在水中的位置來估計噴霧液的含量(見圖 2.)。

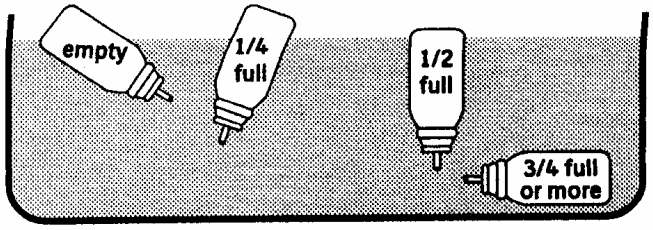

圖 2.

口含器需時常保持清潔並以溫水清洗，若使用肥皂或清潔劑，必須以清水充分沖洗乾淨。

警語：

該塑膠口含器是 BEROTEC 100 微公克定量噴霧液專用，可確保病人每次所接受的劑量是正確的。所以此口含器不可用於其他的定量噴霧液劑，而 BEROTEC N 100 mcg/puff 也不可使用其他口含器，必須使用附於產品上之口含器。

容器為加壓器，不可強力打開或暴露於 50℃以上之溫度。

禁忌

肥大阻塞性心肌病變(hypertrophic obstructive cardiomyopathy)、心跳過速及對 fenoterol hydrobromide 與製劑中不具活性的其他成分過敏者禁用。

特別注意

首次使用 BEROTEC 100 微公克定量噴霧液新處方藥物時，部份病人可能會感覺味道和原含 CFC 處方之藥物不同,所以當病人更換新處方之藥物時須告知病人，也必須告知病人雖然新處方藥物味道不同，但不會影響其安全性或功效。

只有在醫師嚴密監護下 BEROTEC 100 微公克定量噴霧液才可與其他擬交感神經性支氣管擴張劑併用，然而 BEROTEC 可與抗膽鹼性之支氣管擴張劑同時使用。對未完全控制病情的糖尿病患者，曾於最近發作過心肌梗塞、嚴重器質性心臟或血管疾病、甲狀腺機能亢進、親鉻細胞瘤(phaeochromocytoma)的病患，需經醫師謹慎評估其使用之利弊，方可使用 BEROTEC，尤其是當使用劑量超過建議量時。

若患者發生急性且快速惡化的呼吸困難時，應立即請教醫師。

長期使用：

-症狀治療比持續治療更合適。

-患者持續治療時，應重新評估添加或增加抗發炎藥物(如吸入性類固醇藥物)，以控制氣管的發炎現象及避免其長期受損。

請勿因支氣管阻塞情況惡化或不見改善，就一味地增加β_2致效劑如 BEROTEC 100 微公克定量噴霧液的藥物劑量，若長期使用超過建議劑量的β_2致效劑，是不適當的且可能對支氣管造成傷害。持續增加β_2致效劑的劑量治療支氣管阻塞之症狀，可能會降低藥物對疾病的控制效果。在此狀況下，應檢討病人的治療計畫，尤其需要適當的合併抗發炎藥物，以防止病情惡化避免生命受到威脅。

使用β_2致效劑可能發生嚴重的低血鉀症，對於嚴重氣喘患者應特別謹慎，其與黃　呤(xanthine)衍生物、類固醇及利尿劑合併治療時，低血鉀症更有可能發生。此外，對於心律不整之患者，缺氧可能使β_2致效劑引起之低血鉀症更嚴重，這類患者應監測血鉀的濃度。

藥物交互作用

β腎上腺激性藥物、抗膽鹼性藥物及黃　呤衍生物如：theophylline 會增加 fenoterol 的作用，與其他β致效劑類藥物、全身性吸收之抗膽鹼性藥物或黃　呤衍生物併用時，可能增加副作用。

與β阻斷劑併用時，支氣管擴張作用可能嚴重減低。

正以單胺氧化　抑制劑(monoamine oxidase inhibitors)或三環抗抑鬱劑(tricyclic antidepressants)治療的病人使用β腎上腺素性作用藥應謹慎，因為上列藥物可能加強β腎上腺素致效劑作用。

吸入 halogenated hydrocarbon 類之麻醉劑，如：halothane、trichloroethylene 及 enflurane，可能增加β致效劑對心臟血管作用的敏感性。

副作用

BEROTEC 100 微公克定量噴霧液常見的副作用為骨骼肌輕微震顫及精神緊張、頭痛、暈眩、心跳過速及心悸。

以β_2致效劑治療，可能造成嚴重低血鉀症。
與使用其他吸入治療時相同，會有咳嗽、局部刺激、不規則支氣管收縮(比一般少)等症狀產生。
與使用其他β致效劑類藥物相同，可能發生噁心、嘔吐、流汗、虛弱及肌肉痛/肌肉痙攣等症狀，少部份病人在使用高劑量之後可能發生舒張壓下降、收縮壓升高、心律不整等症狀。
已有少數病患發生皮膚反應或過敏反應，特別是過敏性體質的病人。
有幾個病患使用β致效劑類藥物吸入治療會發生心理改變。

懷孕與哺乳

臨床前資料及已有的人體經驗顯示本藥使用於孕婦無不良影響。然而懷孕期間用藥應特別注意，尤其是懷孕的前三個月更需小心。
使用本藥時，應注意 fenoterol 有抑制子宮收縮的作用。
臨床前的研究已顯示 fenoterol 會分泌至乳汁中，授乳的安全性尚未建立。

過量

症狀

過量之預期症狀為β腎上腺素性過度興奮，即藥理作用過度表現，包括所有列於「副作用」的症狀，其中最明顯者為心跳過速、心悸、震顫、高血壓、低血壓、脈搏壓增大、心絞痛、心律不整及潮紅。

治療

可使用鎮靜劑、安神劑，嚴重病例需給予加護醫療。
β接受體阻斷劑可作為解毒劑，尤其以具β1 受體選擇性者為佳，但是支氣管氣喘病人使用時，應考慮其可能增加支氣管阻塞，而必須小心調整劑量。

毒物學

BEROTEC 重複劑量之毒性試驗顯示含 HFA 處方之試驗數據與傳統含 CFC 之處方相似。
在小鼠、大鼠、狗及猴子以口服、靜脈注射、皮下注射、腹腔內注射與吸入等投與方式之急性毒性試驗。口服之 LD50 在成年之嚙齒類動物與兔子為每公斤體重 1600 - 7400 公絲(1600 - 7400 mg/kg BW)，狗為每公斤體重 150 - 433 公絲(150 - 433 mg/kg BW)。以靜脈注射投與上述試驗動物之 LD50 為每公斤體重 34 - 81 公絲(34 - 81 mg/kg BW)。吸入投與的毒性極低。依實驗動物的種類與不同的實驗設計，即使劑量達每公斤體重 670 公絲，也未發現死亡情況。
重複劑量毒性試驗為期 78 週，以口服、皮下注射、靜脈注射、腹腔注射及吸入等方式對小鼠、大鼠及狗投藥。這些慢性毒性試驗之結果如下：在狗、兔子、小鼠及大鼠發現有β擬交感神經作用劑典型的現象(例如：肝醣排空、肌肉內肝醣量減少、血清中鉀濃度降低、心跳過速)。在較高的劑量，如每日每公斤體重 1 公絲(1 mg/kg BW/d)以上的劑量，以各種投與途徑使

用(例如：兔子靜脈注射 4 星期以上)，則在大鼠、小鼠及兔子可觀察到心肌肥大及/或損害。狗對β腎上腺素激性藥物極敏感，劑量在每日每公斤體重 0.019 公絲(0.019 mg/kg BW/d)以上就可見到這些損害。
猴子亞急性吸入試驗顯示 BEROTEC 沒有毒性。
生殖毒性試驗中，吸入投與不會造成大鼠與兔子畸胎及胚胎毒性。Fenoterol hydrobromide 不會損害生育力和飼育。
口服劑量達每日每公斤體重 40 公絲(40 mg/kg BW/d)，對雌雄大鼠生育力無損害。兔子口服日劑量達每公斤體重 25 公絲(25 mg/kg BW)及小鼠口服日劑量達每公斤體重 38.5 公絲(38.5 mg/kg BW)時，無胚胎毒性及致畸性。觀察日劑量為每公斤體重 3.5 公絲(3.5 mg/kg BW/d)及 25 公絲(25 mg/kg BW/d)的大鼠分娩反應，發現死胎及/或新生鼠死亡率會稍微增加。在極高劑量，每日每公斤體重口服 300 公絲(300 mg/kg BW/d)及每日每公斤體重靜脈注射 20 公絲(20 mg/kg BW/d)之情況下，畸形發生率增加。
Fenoterol hydrobromide 體外、體內試驗並未見其有突變反應。
小鼠(口服 18 個月)及大鼠(口服及吸入 24 個月)之致癌性試驗，顯示口服 fenoterol hydrobromide 劑量在每日每公斤體重 25 公絲(25 mg/kg BW/d)時，會誘發小鼠變異性絲狀分裂的平滑肌瘤及大鼠卵巢系膜平滑肌瘤罹患率增加，這是因為β腎上腺素激性藥物在小鼠及大鼠子宮平滑肌細胞局部作用所導致的。而現在的研究顯示這些結果不會發生在人類。其他所有贅瘤的發生被認定是源自於該類動物自然發生的一般型贅瘤，與以 fenoterol 治療無生物學關連。
BEROTEC HFA 和 BEROTEC CFC 對呼吸道具相等且良好的耐受性。
局部耐受性試驗是以靜脈注射、動脈注射、閉合及半閉合皮膚使用於兔子、以 0.05%或 0.1%溶液滴入兔子的結膜袋完成，顯示其耐受性佳。

包裝

100 公撮以下不銹鋼罐裝
10 公撮定量噴霧液(= 200 個定劑量)

製造廠/廠址

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173,
55216 Ingelheim am Rhein, Germany
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

藥商：台灣百靈佳殷格翰股份有限公司
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請存放於兒童伸手不及處！

BASIC PRODUCT INFORMATION 30.07.1999
No. 0237-00

Berotec N 100 mcg/puff Metered Aerosol

Composition
1 metered dose (puff) contains
1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol hydrobromide (= fenoterol hydrobromide) 100 mcg

Properties
Trials with a treatment duration of up to three months involving adult asthmatics and COPD patients, and asthmatic children, in which the HFA formulation and the CFC formulation have been compared have shown the two formulations to be therapeutically equivalent. [105-109]
Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating $beta_2$-receptors in the therapeutic dose range. The stimulation of $beta_1$-receptors comes into effect at a higher dose range. Occupation of $beta_2$-receptors activates adenyl cyclase via a stimulatory G_S-protein. The increase in cyclic AMP activates protein kinase A which then phosphorylates target proteins in smooth muscle cells. This in turn leads to the phosphorylation of myosin light chain kinase, inhibition of phosphoinositide hydrolysis, and the opening of large-conductance calcium-activated potassium channels. There is some evidence that the "maxi-K channel" can be directly activated via the G_S-protein. [37]
Fenoterol relaxes bronchial and vascular smooth muscle and protects against bronchoconstricting stimuli such as histamine, methacholine, cold air, and allergen (early response). After acute administration the release of bronchoconstricting and pro-inflammatory mediators from mast cells is inhibited. Further, an increase in mucociliary clearance [38] has been demonstrated after administration of higher doses of fenoterol.
Higher plasma concentrations, which are more frequently achieved with oral, or even more so, with intravenous administration inhibit uterine motility [39]. Also at higher doses, metabolic effects are observed: Lipolysis, glycogenolysis, hyperglycaemia [40] and hypokalaemia [41], the latter caused by increased K+-uptake primarily into skeletal muscle. Beta-adrenergic effects on the heart such as increase in heart rate and contractility, are caused by the vascular effects of fenoterol, cardiac beta2-receptor stimulation, and at supratherapeutic doses, by beta1-receptor stimulation. Tremor is a more frequently observed effect of beta-agonists. Unlike the effects on the bronchial smooth muscle, the systemic effects of ß-agonists are subject to the development of tolerance [42].
In clinical studies fenoterol was shown to be highly efficacious in manifest bronchospasm [43-46]. It prevents bronchoconstriction following exposure to various stimuli [47] such as exercise [5,48,49] cold air, and the early response following allergen exposure [50].

Pharmacokinetics
The therapeutic effect of BEROTEC is produced by a topical action in the airway. The pharmacodynamics of the bronchodilation produced by BEROTEC are therefore not relevant

to the pharmacokinetics of the active constituent of the preparation. Pharmacokinetic investigation has shown, however, that the HFA formulation and the conventional CFC formulation can be considered equivalent. [110-114]
Following inhalation of fenoterol hydrobromide in obstructive lung diseases, bronchodilatation occurs within a few minutes. The bronchodilator effect lasts 3 –5 hours.
Following inhalation, depending upon the method of inhalation and the system used, about 10 - 30% of the active ingredient released from the aerosol preparation reaches the lower respiratory tract, whereas the remainder is deposited in the upper respiratory tract and in the mouth. As a result, some of the fenoterol, which has been administered by inhalation, enters the gastro-intestinal tract. After inhalation of one puff from a BEROTEC N 100 mcg/puff metered aerosol, an absorption rate of 17% of the dose has been determined. Absorption then follows a biphasic course, 30% of fenoterol hydrobromide being rapidly absorbed with a half-life of 11 minutes, 70% being slowly absorbed with a half-life of 120 minutes [51].
There is no correlation between plasma levels and the pharmacodynamic time response curve following inhalation. The long bronchodilator action following inhalation compared with that following intravenous administration is not supported by the systemic plasma levels [52].
After oral administration, approximately 60% of the fenoterol hydrobromide is absorbed [53]. The percentage, which has been absorbed, undergoes thorough first-pass metabolism with the result that oral bioavailability falls to about 1.5% [43]. This is why the swallowed portion of the active ingredient contributes practically nothing to the systemic plasma level following inhalation.
Systemically administered fenoterol hydrobromide is eliminated according to a 3-compartment model with half-lives of $t_{\alpha 1/2}$ = 0.42 minutes, $t_{\beta 1/2}$ = 14.3 minutes and $t_{\gamma 1/2}$ = 3.2 hours [54].
Metabolic transformation of fenoterol hydrobromide in man occurs almost exclusively by sulphation, predominantly in the intestinal wall.
In its non-metabolised state, fenoterol hydrobromide can pass through the placenta and enter the maternal milk.
There is insufficient data on the effects of fenoterol hydrobromide in the diabetic metabolic state.

Indications
Treat and prevent bronchospasm diseases including bronchial asthma, obstructive bronchitis, chronic bronchitis, emphysema and pulmonary bronchial disorder accompanied with bronchospasm.

Dosage and Administration
Dosage
a) Acute asthma episodes
   1 puff is sufficient for prompt symptom relief in many cases, if breathing has not noticeably improved after 5 minutes, a second dose may be taken.
   If an attack has not been relieved by 2 puffs, further puffs may be required.
   In these cases, patients should consult the doctor or the nearest hospital immediately.
b) Prophylaxis of exercise induced asthma
   1 - 2 puffs for each administration, up to a maximum of 8 puffs per day.
c) Bronchial asthma and other conditions with reversible airways narrowing

If repeated dosing is required, 1 - 2 puffs for each administration, up to a maximum of 8 puffs per day.

In children BEROTEC N 100 mcg/puff metered aerosol should only be used on medical advice and under the supervision of an adult.

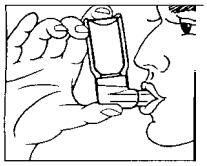
Administration

The correct administration of the metered aerosol is essential for successful therapy [9].

Depress the valve twice before the apparatus is used for the first time.

Before each use the following rules should be observed:

1. Remove protective cap.



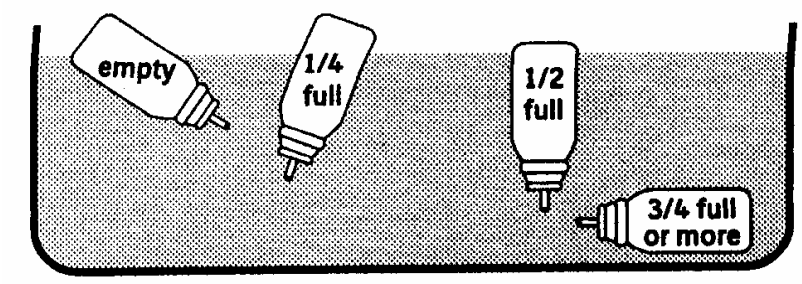
(fig. 1)

2. Breathe out deeply.
3. Hold the metered aerosol as shown in fig. 1, and close lips over the mouthpiece. The arrow and the base of the container should be pointing upwards.
4. Breathe in as deeply as possible, pressing the base of the container firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece and breathe out.
5. Replace the protective cap after use.
6. After not using the metered aerosol for three days the valve has to be actuated once.

The container is not transparent. It is not therefore possible to see when it is empty. The aerosol will deliver 200 doses. When these have all been used the aerosol may still appear to contain a small amount of fluid. The aerosol should, however, be replaced because you may not get the right amount of treatment.

The amount of treatment in your aerosol can be checked as follows:

Remove the aerosol from the plastic mouthpiece and put the aerosol into a container of water. The contents of the aerosol can be estimated by observing its position in the water (see fig. 2)



(fig. 2)

The mouthpiece should always be kept clean and can be washed with warm water. If soap or detergent is used, the mouthpiece should be thoroughly rinsed in clear water.

WARNING:

The plastic mouthpiece has been specially designed for use with BEROTEC N 100 mcg/puff to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other metered aerosol nor must the BEROTEC N 100 mcg/puff be used with any mouthpiece other than the one supplied with the product.
The container is under pressure and should by no account be opened by force or exposed to temperatures above 50°C.

Contraindications
Hypertrophic obstructive cardiomyopathy, tachyarrhythmia [10]. Hypersensitivity to fenoterol hydrobromide or inactive ingredients of the metered aerosol [11].

Special Precautions
When using the new formulation of BEROTEC N 100 mcg/puff for the first time, some patients may notice that the taste is slightly different from that of the CFC-containing formulation. Patients should be made aware of this when changing from one formulation to the other. They should also be told that the formulations have been shown to be interchangeable for all practical purposes and that the difference in taste has no consequences in terms of the safety or the efficacy of the new formulation. [120]
Other sympathomimetic bronchodilators should only be used with BEROTEC N 100 mcg/puff under medical supervision. Anticholinergic bronchodilators may however be inhaled at the same time.
In the following conditions BEROTEC N 100 mcg/puff should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used:
Insufficiently controlled diabetes mellitus [12], recent myocardial infarction, severe organic heart or vascular disorders [13], hyperthyroidism, phaeochromocytoma [14].
In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.
Prolonged use:

- On demand (symptom-oriented) treatment may be preferable to regular use [15].
- Patients should be evaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation and to prevent long-term lung damage [16,17].

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of beta$_2$-agonist containing drugs such as BEROTEC N 100 mcg/puff beyond the recommended dose over extended periods of time [18,19]. The use of increasing amounts of beta$_2$-agonist containing products like BEROTEC N 100 mcg/puff on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control [20]. In this situation, the patient's therapy plan, and in particular the adequacy of the anti-inflammatory therapy, should be reviewed to prevent potentially life threatening deterioration of disease control [21].
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy [22]. Particular caution is advised in severe asthma, as this effect may be potentiated by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. Additionally, hypoxia

may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

Drug Interactions
Beta-adrenergics, anticholinergics [23,24], and xanthine derivatives (such as theophylline [25]) may enhance the effect of fenoterol. The concurrent administration of other beta-mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the side effects [26].
A potentially serious reduction in bronchodilatation may occur during concurrent administration of beta-blockers [27].
Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors [28] or tricyclic antidepressants [29], since the action of beta adrenergic agonists may be enhanced.
Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists [30].

Side Effects [103,104]
Frequent undesirable effects of BEROTEC N 100 mcg/puff are fine tremor of skeletal muscles and nervousness, headache, dizziness, tachycardia and palpitations.
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy.
As with use of other inhalation therapy, cough, local irritation and less common, paradoxical bronchoconstriction [32] have been reported.
As with other beta-mimetics, nausea, vomiting, sweating, weakness and myalgia/muscle cramps [33] may occur. In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmias, particularly after higher doses, may occur.
In rare cases skin reactions or allergic reactions have been reported, especially in hypersensitive patients.
In individual cases psychological alterations have been reported under inhalational therapy with beta-mimetics [34,35].

Pregnancy and Lactation
Pre-clinical data [77-83], combined with available experience in humans have shown no evidence of ill-effects in pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, especially during the first trimester, should be exercised.
The inhibitory effect of fenoterol on uterine contraction should be taken into account [31].
Pre-clinical studies have shown that fenoterol is excreted into breastmilk. Safety during lactation has not been established.

Overdosage
Symptoms
The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, including exaggeration of the known pharmacologic effects, i.e. any of the symptoms listed

under side effects, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias [36] and flushing.

Therapy

Administration of sedatives, tranquillisers, in severe cases intensive therapy.
Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.

Toxicology

Toxicity studies with repeated doses of BEROTEC have shown the toxicological profiles of the HFA formulation and the conventional CFC formulation to be similar. [115-119]
Acute toxicity studies have been undertaken in the mouse, rat, dog and monkey by oral, i.v., s.c., i.p. and inhalation routes. The oral LD50 was evaluated to be in the range of 1600 to 7400 mg/kg bodyweight (BW) in adult rodents [55,56] and rabbits [57] and in dogs between 150 and 433 mg/kg BW [58,59]. Intravenous LD50 for mouse, rat, rabbit and dog was between 34 and 81 mg/kg BW [60,61]. When administered by inhalation, toxicity was very low. Up to 670 mg/kg BW [62], dependent from species and experimental set-up, no mortality was observed.
Repeated dose toxicity studies include the chronic testing in mice, rats and dogs for periods of up to 78 weeks and by varying routes of administration, p.o., s.c., i.v., i.p. and by inhalation. Summarising, the toxicity studies revealed findings in dog, rabbit, mouse and rat, typically after administration of beta-sympathomimetics (e.g. depletion of liver glycogen [63], reduced glycogen content of muscle [64,65], reduced serum potassium levels [66], tachycardia [67]). At higher dosages, myocardial hypertrophy and/or lesions were observed in rat [68], mouse [69], and rabbit at various administration routes from 1 mg/kg BW/d onwards, e.g. rabbits [70] after i.v. administration over a period of 4 weeks. In the dog - most sensitive species to beta-adrenergics - these lesions were discerned from 0.019 mg/kg BW/d [71-73] onwards.
Subacute inhalation studies in monkeys [74,75] revealed no direct substance related toxic effects.
In reproduction toxicity studies, rats and rabbits revealed no teratogenic or embryotoxic changes, when administered by inhalation. Fertility and rearing were not impaired by fenoterol hydrobromide.
When administered perorally, doses up to 40mg/kg BW/d [76] had no deleterious effects on fertility of male and female rats. Daily oral doses up to 25 mg/kg BW in rabbits [77,78], and up to 38.5 mg/kg BW in mice [79] showed neither embryotoxic nor teratogenic effects.
In rats tocolytic effects were observed at doses of 3.5 mg/kg BW/d [80], at 25 mg/kg BW/d [81], a slightly increased foetal and/or neonatal mortality occurred. Extremely high doses of 300 mg/kg BW/d p.o. [82] and 20 mg/kg BW/d i.v. [83] revealed an increased rate of malformations.
Mutagenic activity was not observed when fenoterol hydrobromide was tested in-vitro and in-vivo [84-94].

Carcinogenicity studies in mice (p.o., 18 months [95]) and rats (p.o. [96] and inhal.[97], 24 months) revealed at oral dose levels of 25 mg/kg BW/d fenoterol hydrobromide induced an increased incidence of uterine leiomyomas with variable mitotic activity in mice and mesovarial leiomyomas in rats, recognised effects caused by the local action of beta-adrenergic agents on the uterine smooth muscle cell in mice and rats. Taking into account the present level of research, these results are not applicable to man. All other neoplasias found were considered to be common types of neoplasia spontaneously occurring in the strains used and did not show a biologically relevant increased incidence resulting from treatment with fenoterol.
BEROTEC HFA and BEROTEC CFC have been shown to be equally well tolerated in the respiratory tract.
Local tolerance studies with i.v., i.a., occlusive and semiocclusive dermal administration to rabbits [98-100] and instillation of a 0.05 or 0.1 % solution into the conjunctival sac of rabbits [101] were well tolerated.

Availability
Metered Aerosol

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173,
552216 Ingelheim am Rhein, Germany
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Store in a safe place out of the reach of children!