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

賦形劑

1,1,1,2-Tetrafluoroethane (HFA 134a)、無水檸檬酸、純水、絕對酒精

藥理性質

藥物類別：阻塞性呼吸道疾病治療用藥，選擇性 ß2-腎上腺素受體促效劑。

ATC 代碼：R03AC04

BEROTEC 是有效的支氣管擴張劑，使用在急性氣喘和可逆性呼吸道狹窄的其他狀況，例如伴隨或未伴隨肺氣腫之慢性阻塞性支氣管炎等。經口投與 BEROTEC 後數分鐘內即可作用，作用時間達 8 小時。

阻塞性肺疾病人吸入 fenoterol hydrobromide 後數分鐘內即有支氣管擴張作用，此作用可維持 3 至 5 小時。

作用機制

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，活化腺嘌呤環狀酶(adenyl cyclase)，增加 cAMP 活化蛋白激酶 A (protein kinase A)，使平滑肌細胞中的標的蛋白磷酸化，依次促使 myosin light chain 激酶磷酸化，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。

藥物效力學

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(0.6 mg)的 fenoterol 後，可增加黏膜纖毛的清除效果。

口服，尤其靜脈注射後常得到較高的血中濃度，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。β致效劑對心臟的作用如心跳與心收縮的增加是透由對血管的作用及心臟β_2 受體的興奮作用以及在高於治療劑量

時，經由有β_1受體興奮性之作用。與其他的β致效劑相同，曾通報 QT 延長的案例。這種事件通常為分散事件並且都在 fenoterol 噴霧劑量高於建議劑量時觀察到。

然而，以吸入液給藥之全身暴露量可能高於在推薦劑量之 MDI 給藥(請參閱“用法用量”)，其臨床意義尚未被建立。β致效劑常見震顫反應。

臨床研究顯示 fenoterol 可有效治療支氣管痙攣，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

經靜脈、吸入投與或口服 fenoterol 的藥動學資料已被研究過。BEROTEC 的治療效果來自於藥物在呼吸道的局部作用，因此血漿中的藥物濃度與支氣管擴張效用沒有關聯。

吸入 Fenoterol 後，大約 10 – 30%的主成分會由定量噴霧劑釋出到達下呼吸道，此與吸入方法和吸入裝置的不同而有差異。剩餘部份則留在上呼吸道及口中，然後被吞入。

吸收

吸入 BEROTEC 定量噴霧液後之絕對生體可利用率為 18.7 %。在肺部的吸收為雙相的， 30%劑量的 fenoterol hydrobromide 迅速被吸收，半衰期為 11 分鐘，而被緩慢吸收的 70%，其半衰期為 120 分鐘。

以定量噴霧液(HFA-MDI)單次劑量吸入 fenoterol 200 µg 後 15 分鐘(t_{max})，達最高血漿濃度(幾何平均)為 66.9 pg/mL。

口服後約 60%劑量的 fenoterol hydrobromide 被吸收，被吸收之藥物經由廣泛的首渡代謝，其口服之生體可用率為 1.5%。因此，吸入後被吞入的主成分對血漿濃度的影響很小。

分佈

Fenoterol 廣泛分佈於全身。靜脈投與(V_{ss})後，穩定狀態之分佈體積為 1.9 – 2.7 L/kg。靜脈投與後，fenoterol 是經由三室的(3-compartment)藥動學模式進行排除。半衰期分別為 t_α = 0.42 分鐘，t_β = 14.3 分鐘，t_γ = 3.2 小時。40 至 50%與血漿蛋白結合。

生物轉化（Biotransformation）

Fenoterol hydrobromide 在人體經由結合成尿苷酸化物(glucuronides)及硫酸化物(sulphates)而廣泛地被代謝。口服後，fenoterol 主要經由硫酸化被代謝。此將原化合物不活性化的代謝作用在腸壁即已開始進行。

排泄

靜脈投與後，平均總清除率為 1.1-1.8 L/min，其中大部份(約 85%)是經由包括膽汁排泄在內的生體轉換。經腎臟清除的 fenoterol (0.27 L/min)相當於全身劑量平均總清除率的約 15%。考量藥物和血漿蛋白結合的程度，腎臟清除的數值顯示 fenoterol 除了經絲球體過濾外，還會被腎小管分泌。

經口或靜脈投與後的總放射活性，經尿液排出者分別為劑量的 39%和 65%。48

小時內經糞便排出的放射活性則分別為 40.2%和 14.8%。經口投與後，劑量的 0.38%以原化合物從尿液排出，然而靜脈投與後，15%以原化合物排出。吸入一個定劑量後，在 24 小時內，劑量的 2%以原型經由腎臟排出。
Fenoterol hydrobromide 的原型藥物可穿透胎盤且會進入母乳中。
Fenoterol hydrobromide 在糖尿病病人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

本藥須由醫師處方使用

a)急性氣喘發作和其他伴隨有支氣管痙攣之可逆性呼吸道狹窄的情況

對大多數的病人，一個定劑量即可緩解症狀，若吸入 5 分鐘後呼吸沒有明顯的改善，可投與第二個定劑量，每天最多不得投與超過 8 個定劑量。
投與第二個定劑量後，若治療仍未改善，可能需要再投與數個定劑量，此時應立即請教醫師或就近送醫(參見特別警語及注意)。

b) 預防運動引發的氣喘

在運動前給與 1 – 2 個定劑量，每天不得超過 8 個定劑量。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。

使用說明

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。
   如需給與第二個定劑量，請依步驟 2 至 4 重複操作。
5. 使用後蓋上護蓋。

6. 此定量噴霧液若 3 天未使用，必須將活塞再啟動(actuated)。
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 個定劑量，當 200 個定劑量都被使用後，可能仍有少量液體留存，但因無法確定每個劑量都含有足夠的治療含量，請勿再使用。

每週至少應清潔吸入器的口含器一次。
吸入器的口含器務必要保持清潔，以確保藥品不會堆積而阻塞噴霧劑。
清潔吸入器的步驟為：首先將防塵蓋取下，把藥罐從口含器移除。以溫水洗滌口含器，直到沒有藥物阻塞和沒有可見的灰塵。

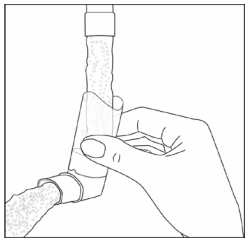


圖 2.

清潔後，甩乾口含器並令其陰乾，勿使用任何加熱方式。當口含器乾燥後，將藥罐和防塵蓋組裝回原樣。

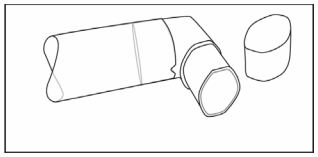


圖 3.

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
BEROTEC 禁用於有下列狀況的病人：

- 肥大阻塞性心肌病變(hypertrophic obstructive cardiomyopathy)
- 心跳過速

- 對 fenoterol hydrobromide 或本藥任一賦形劑過敏之病人。

特別警語及注意

在下列情況之下，需經醫師謹慎評估其使用之利弊，方可使用 BEROTEC，尤其是當使用最高建議劑量時：

- 對未完全控制病情的糖尿病人
- 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)

<u>反常性支氣管痙攣</u>

與其他吸入型藥物相同，BEROTEC 亦可引起可能危及性命之反常性(paradoxical)支氣管痙攣。若發生反常性支氣管痙攣，應立即停用 BEROTEC 並以其他療法替代。

<u>心血管作用</u>

使用擬交感神經性藥物，包括 BEROTEC，可能出現心血管作用。有一些來自上市後資料及已發表文獻的證據顯示，少數病例的心肌缺血與腎上腺素性β-致效劑之使用有關。對合併有嚴重心臟疾病(如缺血性心臟病、心律不整或嚴重心臟衰竭)且正接受 BEROTEC 治療的病人，應給予下列警示：若出現胸痛或心臟病惡化的其他症狀，應尋求醫師的建議。應注意症狀的評估，例如呼吸困難和胸痛，因為此可能起因於呼吸系統或心臟。

<u>低血鉀症</u>

使用β_2-致效劑治療時可能需注意嚴重低血鉀症之可能性。與黃嘌呤衍生物、皮質類固醇和利尿劑併用時可能誘導低血鉀症更嚴重，嚴重氣喘病人應特別注意。此外，缺氧可能加強低血鉀對心律之影響，低血鉀症可能使得正在服用 digoxin 之病人更易產生心律不整，此種情況之下，建議檢測血鉀濃度。

<u>急性漸進性呼吸困難</u>

應告知病人，若發生急性呼吸困難或呼吸困難急速惡化時應立即就醫。

<u>一般警語</u>

- 症狀治療(有需要時才用藥)比持續治療更合適。
- 病人持續治療時，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的肺部傷害。

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 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。若持續增加β_2致效劑的劑量來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。

併用擬交感神經性與抗膽鹼性支氣管擴張劑

在醫師嚴密監護下，BEROTEC 定量噴霧液才可與其他擬交感神經性支氣管擴張劑併用(參見藥物相互作用一節)，但可與抗膽鹼性支氣管擴張劑同時使用。

干擾檢測或其他診斷

使用 BEROTEC 可能會使非臨床物質濫用的檢驗因 fenoterol 而呈現陽性反應的結果，例如在運動員表現提升之情況下所進行的檢驗(禁藥檢測)。

交互作用

β腎上腺激性藥物、抗膽鹼性藥物及黃嘌呤衍生物如 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嘌呤衍生物併用時，可能增加副作用。

與黃嘌呤衍生物、皮質類固醇和利尿劑併用時可能使β_2-致效劑誘導之低血鉀症更嚴重，嚴重呼吸道阻塞病人應特別注意（參見特別警語及注意一節）。

與β阻斷劑併用時，支氣管擴張作用可能嚴重減低。

正以單胺氧化酶抑制劑(monoamine oxidase inhibitors)或三環抗抑鬱劑(tricyclic antidepressants)治療的病人，使用β腎上腺素性作用藥時應謹慎，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。

特定族群的使用

生育力、懷孕與哺乳

懷孕

非臨床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。

授乳

非臨床的研究已顯示 fenoterol 會分泌至乳汁中，授乳的安全性尚未建立。因此，授乳婦女應小心使用 BEROTEC。

生育力

目前並無 fenoterol 對生育力之影響的臨床資料。以 fenoterol 所進行的非臨床研究顯示本藥對於生育力無不良影響(參見毒物學之欄位)。

駕駛及操作機械

目前尚未進行過任何探討本品對駕駛和機械操作能力之影響的研究。

不過，應告知病人暈眩症狀之不良反應曾發生於臨床試驗。因此，建議在開車或操作機械時應謹慎。

不良反應

與所有吸入治療相同，BEROTEC 可能造成局部刺激症狀。

不良反應摘要表

以下不良反應皆透過臨床試驗與上市後藥物安全監測中取得。

系統器官類別	**不良反應**
免疫系統異常	過敏
代謝及營養異常	低血鉀症；也可能含嚴重案例
精神異常	激動 精神緊張
神經系統異常	震顫 頭痛 暈眩
心臟異常	心肌缺血 心律不整 心跳過速 心悸
呼吸、胸腔及縱膈異常(僅適用於吸入性使用時)	逆理性支氣管痙攣(paradoxical bronchospasm)、咳嗽、喉嚨刺激
胃腸異常	噁心 嘔吐
皮膚及皮下組織異常	多汗症 皮膚反應例如皮疹、癢、蕁麻疹
骨骼肌肉、結締組織及骨骼異常	肌肉痙攣 肌肉痛 肌肉無力
調查研究	收縮壓升高 舒張壓下降

過量

症狀

過量之預期症狀為β腎上腺素性質之過度興奮，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。

代謝性酸中毒和低血鉀症也曾發生於 Fenoterol 超過 BEROTEC 核准適應症之建議劑量時。

治療

應停止 BEROTEC 的治療，且應考慮施行酸鹼值和電解質的監測。

可使用鎮靜劑，嚴重病例可能需給予加護醫療。

β接受體阻斷劑可作為解毒劑，尤其以具β_1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

單一劑量毒性

口服之 LD_{50} 的數值在成年之小鼠、大鼠、兔子的範圍為每公斤 1600 - 7400 公絲(1600 - 7400 mg/kg)，在狗為每公斤 150 - 433 公絲(150 - 433 mg/kg)。以靜脈注射投與上述試驗動物之 LD_{50} 為每公斤 30 - 81 公絲(30 - 81 mg/kg)。吸入投與的急性毒性在大鼠、狗、猴子極低。依不同的實驗條件，吸入劑量在每公斤 0.58 - 670 公絲，並未發現死亡的情況。

重複劑量毒性

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。這些毒性試驗之結果顯示對這些種類的動物有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)。在每日每公斤體重 1 公絲(1 mg/kg /day)以上的劑量，以各種投與途徑使用，在大鼠、小鼠及兔子可觀察到心肌肥大及/或損害。狗是對β腎上腺素激性藥物最為敏感之物種，吸入劑量在每日每公斤體重 0.019 公絲(0.019 mg/kg /day)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

吸入投與的生殖毒性試驗顯示不會造成大鼠與兔子畸胎及胚胎毒性，而且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 /day)，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/day)及小鼠口服日劑量達每公斤體重 38.5 公絲(38.5 mg/kg/day)時，無胚胎毒性及致畸性。

觀察日劑量為每公斤體重口服 3.5 公絲(3.5 mg/kg /day)及 25 公絲(25 mg/kg /day)的大鼠，會有抑制分娩的效應，亦發現死胎及/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 /day)及每日每公斤體重靜脈注射 20 公絲(20 mg/kg /day)之情況下，畸形發生率增加。

基因毒性

Fenoterol hydrobromide 並未顯示在體外、體內試驗有致突變之效應。

致癌性

在致癌性試驗中，經口給藥(小鼠口服 18 個月，大鼠口服 24 個月)及吸入給藥(大鼠吸入 24 個月)，顯示口服劑量在每日每公斤體重 25 公絲(25 mg/kg /day)時，會誘發小鼠具不同程度有絲分裂活性的子宮肌瘤及大鼠卵巢系膜平滑肌瘤罹患率

增加。這些現象是因為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。

局部耐受性

以不同的給藥方式(靜脈注射、動脈注射、皮膚、眼)所做的局部耐受性試驗顯示 fenoterol hydrobromide 的耐受性佳。

包裝

100ml 以下不銹鋼罐裝
10ml 定量噴霧液(= 200 個定劑量)

儲存條件

請存放於 30˚C 以下。

請存放於兒童伸手不及處。

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
地址：台北市中山區民生東路三段 2 號 12 樓

11 APR 2019

修訂日期：2021 年 03 月
核定日期：2021 年 09 月

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

Excipients

1,1,1,2-Tetrafluoroethane (HFA 134a), citric acid anhydrous, water purified, ethanol absolute

Pharmacological Properties

Pharmacotherapeutic group: Adrenergics for inalative use in obstructive airway diseases, selective beta-2-adrenoreceptor agonists

ATC code: R03AC04

BEROTEC is an effective bronchodilator for use in acute asthma and in other conditions with reversible airway narrowing such as chronic obstructive bronchitis with or without pulmonary emphysema. After oral administration BEROTEC acts within a few minutes with a duration of action up to 8 hours.

Following inhalation of fenoterol hydrobromide in obstructive lung diseases, bronchodilatation occurs within a few minutes. The bronchodilator effect lasts 3 -5 hours.

Mode of Action

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.

Pharmacodynamics

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 has been demonstrated after administration of higher doses of fenoterol(0.6 mg).

Higher plasma concentrations, which are more frequently achieved with oral, or even more so, with intravenous administration inhibit uterine motility. Also at higher doses, metabolic effects are observed: Lipolysis, glycogenolysis, hyperglycaemia and hypokalaemia, 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 $beta_2$-receptor stimulation, and at supratherapeutic doses, by $beta_1$-receptor stimulation. As with other beta-adrenergic agents, QTc prolongation has been reported. For fenoterol MDIs these events were discrete and observed at doses higher than recommended. However, systemic exposure after administration with the nebuliser solution might be higher than with recommended

MDI doses (refer to dosage and administration). The clinical significance has not been established. Tremor is a more frequently observed effect of beta-agonists.
In clinical studies fenoterol was shown to be highly efficacious in manifest bronchospasm. It prevents bronchoconstriction following exposure to various stimuli such as exercise cold air, and the early response following allergen exposure.

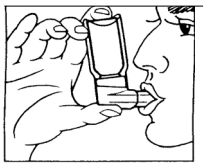
Pharmacokinetics
The pharmacokinetics of fenoterol were studied after intravenous, inhaled and oral dosing.
The therapeutic effect of BEROTEC is produced by local action in the airway. Thus, drug concentrations in plasma are not necessarily correlated with a bronchodilatory effect.
Following inhalation, 10 - 30% of the active ingredient released from the aerosol preparation reaches the lower respiratory tract, depending on the method of inhalation and the system used. The remainder is deposited in the upper respiratory tract and in the mouth and is subsequently swallowed.
Absorption
The absolute bioavailability of fenoterol following inhalation from BEROTEC metered aerosol is 18.7%. Absorption from the lung follows a biphasic course. 30% of the fenoterol hydrobromide dose is rapidly absorbed with a half-life of 11 minutes, and 70% is slowly absorbed with a half-life of 120 minutes.
Maximum plasma concentrations (geometric mean) following inhalation of a single dose of 200 µg fenoterol via metered aerosol (HFA-MDI) was 66.9 pg/mL with a tmax-value of 15 minutes).
After oral administration, approximately 60% of the fenoterol hydrobromide dose is absorbed. The amount absorbed undergoes extensive first-pass metabolism resulting in an oral bioavailability of about 1.5%. Thus, the contribution of the swallowed portion of the active ingredient to the plasma concentration following inhalation is minor.
Distribution
Fenoterol distributes widely throughout the body. The volume of distribution at steady state following intravenous administration (Vss) is 1.9 – 2.7 L/kg. The disposition of fenoterol in plasma following intravenous administration is adequately described by a 3-compartment pharmacokinetic model.The half-lives are $t\alpha = 0.42$ minutes, $t\beta = 14.3$ minutes, and $t\gamma = 3.2$ hours. The plasma protein binding is 40 to 55%.
Biotransformation
Fenoterol undergoes extensive metabolism by conjugation to glucuronides and sulphates in humans. Following oral administration, fenoterol is metabolised predominantly by sulphation. This metabolic inactivation of the parent compound starts already in the intestinal wall.
Excretion
Biotransformation including biliary excretion accounts for the major part (approximately 85%) of the mean total clearance which is 1.1-1.8 L/min following intravenous administration. The renal clearance of fenoterol (0.27 L/min) corresponds to about 15% of the mean total clearance of a systemically available dose. Taking into account the fraction of drug bound to plasma protein, the value of renal clearance suggest tubular secretion of fenoterol in addition to glomerular filtration.
Total radioactivity excreted in urine following oral and intravenous administration is approximately 39% and 65% of the dose, and total radioactivity excreted in faeces is 40.2% and 14.8% of the dose within 48 hours, respectively. 0.38% of the dose is excreted as parent

compound in urine after oral administration, whereas 15% is excreted unchanged following intravenous administration. Following inhalation from a metered dose inhaler, 2% of the dose is excreted renally unchanged within 24 hours.
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
The product should be used by physician prescription.
Dosage
a) Acute asthma episodes and other conditions with reversible airway narrowing
1 puff is sufficient for prompt symptom relief in most cases. If breathing has not noticeably improved after 5 minutes, a second dose may be taken, up to a maximum of 8 puffs per day.
If an attack has not been relieved by 2 puffs, further puffs may be required.
In this situation, patients should be advised to consult the physician or to go to the nearest hospital immediately (see section special warnings and precautions).
b) Prophylaxis of exercise induced asthma
1 - 2 puffs prior to exercise, 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.

Instructions for use/handling
The correct administration of the metered aerosol is essential for successful therapy.
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.
2. Breathe out deeply



(fig. 1)

.
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.
   If a second inhalation is required, the same action (steps 2-4) should be repeated.

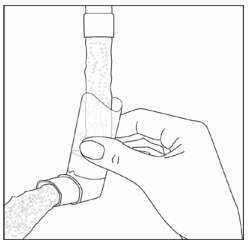
5. Replace the protective cap after use.
6. After not using the metered aerosol for three days the valve has to be actuated once.

The container is not transparent. It is therefore not possible to see when it is empty. The aerosol will deliver 200 puffs. When the labelled number of doses have been used the aerosol may still appear to contain a small amount of fluid. The aerosol should, however, be replaced so that you can be certain that you are getting the right amount of your medicine in each puff.

Clean your mouthpiece at least once a week.

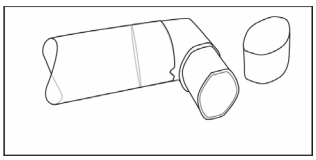
It is important to keep the mouthpiece of your inhaler clean to ensure that medicine does not build up and block the spray.

For cleaning, first take off the dust cap and remove the canister from the mouthpiece. Rinse warm water through the mouthpiece until no medication build-up and/or dirt is visible.



(fig. 2)

After cleaning shake out the mouthpiece and let it air-dry **without** using any heating system. Once the mouthpiece is dry, replace the canister and the dust cap.



(fig. 3)

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

BEROTEC is contraindicated in patients with:

- hypertrophic obstructive cardiomyopathy,
- tachyarrhythmia.

- hypersensitivity to fenoterol hydrobromide or to any of the excipients of the product.

Special Warnings and Precautions

In the following conditions BEROTEC should only be used after careful risk/benefit assessment, especially when highest recommended doses are utilized:

- insufficiently controlled diabetes mellitus
- recent myocardial infarction
- severe organic heart or vascular disorders
- hyperthyroidism
- phaeochromocytoma

Paradoxical bronchospasm

As with other inhaled medicines BEROTEC may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs BEROTEC should be discontinued immediately and substituted with an alternative therapy.

Cardiovascular effects

Cardiovascular effects may be seen with sympathomimetic drugs, including BEROTEC. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists.

Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving BEROTEC should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease.

Attention should be paid to assessment of symptoms as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalaemia

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe asthma, as hypokalaemia may be potentiated by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin.

It is recommended that serum potassium levels are monitored in such situations.

Acute progressive dyspnoea

The patient should be advised to consult a physician immediately in the case of acute, rapidly worsening dyspnea.

Particular warning for regular use

- On demand (symptom-oriented) treatment is preferable to regular use.
- Patients must 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.

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of $beta_2$-agonist containing drugs such as BEROTEC beyond the recommended dose over extended periods of time. The use of increasing amounts of $beta_2$-agonist containing products like BEROTEC on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. 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.

Concomitant use with sympathomimetic and anticholinergic bronchodilators

Other sympathomimetic bronchodilators should only be used with BEROTEC under medical supervision (see section Interactions). Anticholinergic bronchodilators may however be inhaled at the same time.

Interferance with laboratory tests or other diagnostic measures

The use of BEROTEC may lead to positive results on fenoterol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Interactions

Beta-adrenergics, anticholinergics, and xanthine derivatives (such as theophylline) may enhance the effects of fenoterol. The concurrent administration of other beta-mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the side effects.

Hypokalaemia induced by $beta_2$-agonists may be increased by concomitant treatment with xanthine derivatives, corticosteroids, and diuretics. This should be taken into account particularly in patients with severe airway obstruction (see section Special warnings and precautions).

A potentially serious reduction in bronchodilatation may occur during concurrent administration of beta-blockers.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, 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.

Use in Specific Populations

Fertility, Pregnancy and Lactation

Pregnancy

Nonclinical data, combined with available experience in humans have shown no evidence of adverse effects of BEROTEC 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.

Lactation

Nonclinical studies have shown that fenoterol is excreted into breastmilk. Safety during breastfeeding has not been established. Caution should be exercised when BEROTEC is administered to a nursing woman.

Fertility

Clinical data on fertility are not available for fenoterol. Nonclinical studies performed with fenoterol showed no adverse effect on fertility (see section Toxicology).

Driving and Using Machines

No studies on the effect on the ability to drive and use machines have been performed.

However, patients should be advised that symptoms such as dizziness have been reported in clinical trials. Therefore, caution should be recommended when driving a car or operating machinery.

Adverse Reactions

As with all inhalation therapy BEROTEC may show symptoms of local irritation.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during use of BEROTEC in clinical trials and during the post-marketing experience.

System Organ Class	**Adverse Reactions**
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Hypokalaemia including serious hypokalaemia
Psychiatric disorders	Agitation Nervousness
Nervous system disorders	Tremor Headache Dizziness
Cardiac disorders	Myocardial ischaemia Arrhythmia Tachycardia Palpitations
Respiratory, thoracic and mediastinal disorders (only applicable to inhalative)	Bronchospasm paradoxical Cough Throat irritation
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous tissue disorders	Hyperhidrosis Skin reaction such as rash, pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	Muscle spasm Myalgia Muscular weakness
Investigations	Blood pressure systolic increased Blood pressure diastolic decreased

Overdose

Symptoms

The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias and flushing.

Metabolic acidosis and hypokalaemia have also been observed with fenoterol when applied in doses higher than recommended for the approved indications of BEROTEC.

Therapy
Treatment with BEROTEC should be discontinued. Acid base and electrolyte monitoring should be considered.
Administration of sedatives and, in severe cases intensive therapy may be needed.
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
Single-dose toxicity
The oral LD_{50} values in adult mice, rats and rabbits were in the ranges of 1600 - 7400 mg/kg and 150 - 433 mg/kg in dogs. Intravenous LD_{50} values for mouse, rat, rabbit and dog were between 30 and 81 mg/kg. The acute toxicity after inhalation was very low in rats, dogs and monkeys. Depending on the experimental set-up, mortality was not observed at inhalation doses of 0.58 - 670 mg/kg.
Repeat-dose toxicity
Repeat-dose toxicity studies were performed in mice, rats and dogs for periods of up to 78 weeks and by varying routes of administration (peros, subcutaneous, intravenous, intraperitoneal, inhalation).
Summarising, these toxicity studies revealed findings in the respective species typical for administration of beta-sympathomimetics (e.g. depletion of liver glycogen, reduced glycogen content of muscle reduced serum potassium levels, tachycardia). Myocardial hypertrophy and/or lesions were observed in rat, mouse, and rabbit at various administration routes at doses > 1 mg/kg/day. In the dog – the most sensitive species to beta-adrenergics - these lesions were discerned at inhalation doses > 0.019 mg/kg/day onwards. Subacute inhalation studies in monkeys revealed no direct substance related toxic effects.
Reproduction toxicity
Inhalation reproduction toxicity studies in rats and rabbits revealed no teratogenic or embryotoxic changes and fertility and rearing were not impaired. Oral doses up to 40mg/kg/day had no deleterious effects on male or female fertility in rats. Oral doses up to 25 mg/kg/day in rabbits, and up to 38.5 mg/kg/day in mice showed neither embryotoxic nor teratogenic effects. In rats tocolytic effects were observed at doses of 3.5 mg/kg/day p.o. and at 25 mg/kg/day, a slightly increased fetal and/or neonatal mortality occurred. Extremely high doses of 300 mg/kg/day peros and 20 mg/kg/day i.v. revealed an increased rate of malformations.
Genotoxicity
Fenoterol hydrobromide did not show any mutagenic activity *in vitro* and *in vivo*.
Carcinogenicity
Carcinogenicity studies were performed after oral (mouse, 18 months, rat, 24 months) and inhalation administration (rat, 24 months). At oral doses of 25 mg/kg/day an increased incidence of uterine leiomyomas with variable mitotic activity in mice and mesovarial leiomyomas in rats were observed.
These findings are recognised effects caused by the local action of beta-adrenergic agents on the uterine smooth muscle cell in mice and rats. These results are not believed to be 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.

Local tolerance

In local tolerance studies with different amplication routes (i.v., i.a., dermal, ocular) fenoterol hydrobromide was well tolerated.

Availability

Metered aerosol: pack of 100 ml below in steel can.

10 ml metered aerosol = 200 puffs

Storage conditions

Store below 30°C.

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

Mfd. by
Boehringer Ingelheim Pharma GmbH & Co. KG
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55216 Ingelheim am Rhein, Germany
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

11 APR 2019