Berotec® N
100mcg/puff Metered Aerosol
成分
每一片含
1-(3,5-di-hydroxy-phenyl)-2-[1-(4-hydroxy-benzyl)-ethyl]-amino-ethanolhydrobromide (= fenoterol hydrobromide) 100mcg

性質
以罹患氣喘及COPD之成年人及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，在治療用量下會選擇性的刺激β2受體，較高劑量下才會刺激β1受體，與β2受體結合後刺激GS-蛋白，活化腺嘌呤核苷酸(Adeny cyclase)，增加cAMP活化蛋白激酶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 phosphorylase酸化，抑制phosphoinoside水解，而開啓大傳導性，鈣離子活化之鈣離子通道(large-conductance calcium-activated potassium channels)，有些證據證實鈣離子通道(Max K Channel)可直接被GS-蛋白活化。

Fenoterol松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、methylcholine、冷空氣及過敏原(早期反應)。緊急給薬後，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。

口服及靜脈注射後其血中濃度，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、高血糖和低血糖鉀。低血鉀症主要因骨胳肌對鈣離子之吸收增加而引起。Fenoterol興奮心β2受體，增加心跳速率與心收縮力；在高於治療用量時，有β1, β2受體興奮性之作用。β效應劑常見震顫反應，不同於對支氣管平滑肌的作用，β效應劑之全身性作用會產生藥性。

臨床研究顯示fenoterol治療支氣管叢癱極有效，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的藥動學沒有關聯，藥動學的試驗已顯示，含HFA處方與傳統含CFC處方之療效相同。

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，依吸入方法與裝置不同而有差異，大約10-30%的主成分會由定量噴霧劑吸入及達下呼吸道，剩餘部份則留在上呼吸道及口中，因此，部份經吸入與噴霧器的fenoterol會進入胃腸道，已知吸入一個噴霧劑量之BEROTEC 100微克定量噴霧液之吸收率為17%。吸收為變相的，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過代謝後，其口服之生體可用率爲15%，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，是經由三室模擬式進行排除(t1/2α = 0.42分鐘，t1/2β = 14.3分鐘，t1/2γ = 3.2小時)。Fenoterol hydrobromide在人體內幾乎都是經由硫酸化進行代謝轉換，主要是於小腸壁進行。

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足。
用法用量

用法

a) 急性氣喘發作
對大多數的患者，一個定劑即可緩解症狀，若吸入5分鐘後呼
吸沒有明顯的改善，可接第2個定劑。接第2個定劑後，
若症狀仍未改善，可再接第3個定劑。此時應立即請教
醫師或就近求診。

b) 預防運動引發的氣喘

每次1－2個定劑，每天不得超過8個定劑。

c) 支氣管性氣喘或他任何可逆性呼吸道窄窄情況若需要重覆接與

每次1－2個定劑，但每天不得超過8個定劑。

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

用法

為了達成治療的治癒，應正確操作定量噴霧液装置。

該装置在首次使用之前，須徹底洗淨。

每次使用應注意以下規則：

1. 移去蓋子
2. 深深吐氣
3. 如圖1所示握拿定劑噴霧液，並以雙唇閉口含口器，將頭和容器
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，然後自口中移去口器後呼氣。

5. 使噴霧液品蓋上蓋子。

容器不透明，因此無法看出內容物何时被用完。此噴霧液可提供
200個劑量，當200個劑量都被使用後，可能仍有少量液體存
留，此時不可使用，應即再使用新容器。

噴霧器中的治療含量，可依照下列方法檢查：

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

2.

口器內需常保持清潔並以溫水清洗，若使用肥皂或清潔劑，必
須以清水沖洗乾淨。

警告

該噴霧口器是BEROTEC 100微克定量噴霧液專用，可確保病
人每次所接的含量是正確的。所以此口器不可用於其他
定量噴霧液，而BEROTEC N 100 mcg/puff也不可使用其他口器
，必須使用附於產品上的口器。

容器為加裝器，不可強力打開或暴露於50℃以上之溫度。

禁忌

肥大細胞性心肌病變（hypertrophic obstructive cardiomyopathy）、心跳過速及對fenoterol hydrobromide與製劑
中及具活性的其他成分過敏者禁用。

特別注意

首次使用BEROTEC 100微克定量噴霧液新處方藥物時，部份
人會有不適感，包括CFC處方藥物不同，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及效果。只有在醫師密切監護下
使用BEROTEC 100微克定量噴霧液才可與其他擬交感神經性支氣管
擴張藥併用，然而BEROTEC可與抗腫脹性之支氣管擴張劑同時用
而已使用量超過建議劑量時，在未完全控制病情的療效病者
，可能會發生心衰竭、心律不整或心動過速（phaeochromocytoma）的反應，需要
經醫師評估其使用之利弊，方可使用BEROTEC。

當患者發生急性和快速惡化的呼吸困難時，應立即請教醫師。

長期使用

- 藥療治療比補藥治療更合適。
- 患者持續治療時，應定期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危害。
請勿因支氣管阻塞情況惡化或不見改善，就一味地增加β₂致效劑如
BEROTEC 100 微克克定量噴霧液的藥物劑量，若長期使用超過建議
劑量的β₂致效劑是不適當的且可能對支氣管造成傷害。持續增加
β₂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β₂致效劑可能發生嚴重的低血鈣症，對於嚴重氣喘患者應特別
謹慎，其與黃嘌呤(xanthine)衍生物、類固醇及利尿劑合併治
療時，血鈣症有可能發生。此外，對於心律不整之患者，缺
氧可能使β₂致效劑引起之低血鈣症更嚴重。這類患者應監測血鈣
的濃度。

藥物交互作用
β腎上腺素興奮藥物、抗膿皰性藥物及黃嘌呤衍生物如：
théophylline會增加fenoterol的作用，與其他β致效劑類藥物、
全身性吸收之抗膿皰性藥物或黃嘌呤衍生物併用時，可能增加副
作用。
與β阻斷劑併用時，支氣管擴張作用可能顯著減低。
正以單胺氧化酶抑制劑(monooamine oxidase inhibitors)或三環抗
暈劑(tricyclic antidepressants)治療的病人使用β腎上腺素性
作用藥物應謹慎，因未薈藥物可能加劇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致效劑對心臓血管作
用的敏感性。

副作用
BEROTEC 100 微克克定量噴霧液常見的副作用為骨骼肌輕微震顫
及精神張繫、頭痛、畏光、心悸過速及心悸。
以β₂致效劑治療，可能造成嚴重低血鈣症。
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。

懷孕與授乳
臨床前資料及已有的人體經驗顯示本藥使用於懷孕無不良影響。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
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、脈搏變大、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β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

BHEROTEC重複剂量之毒性試驗顯示HFA處方之試驗數據與傳統含CFC之處方相似。

在小鼠、大鼠、狗及敘子以口服、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在成年的齲齒類動物與家兔之每公斤體重1600~7400公絲(1600~7400 mg/kg BW)，均為每公斤體重150-433公絲(150-433 mg/kg BW)。以靜脈注射投與上述試驗動物之LD50之為每公斤體重34~81公絲(34~81 mg/kg BW)。吸入投與的毒性極低。低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。

重複投與性試驗為期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、鼠子及鼠子發現有B腫瘤變異性神經作用劑與類的現象(例如: 肝腫排空、肌肉內肝腫塊變少、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B腫瘤變異性毒物極敏感，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。

鼠子亞急性吸入試驗顯示BHEROTEC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。Fenotrol hydrobromide不會損害生育力和飼育。口服劑量達每日每公斤體重60公絲(60 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35公絲(35 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)的小鼠分飼，發現胚胎及/或新生死亡率會稍微增加。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)之情況下，畸形發生率增加。

Fenotrol 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)之致腫癌試驗，顯示口服fenotrol hydrobromide劑量在每日每公斤體重25公絲(25 mg/kg BW)時，會誘發小鼠變異性絲狀分裂的平滑肌腫瘤及大鼠卵巢囊腺瘤平滑肌腫瘤罹患率增加，這是因為B腫瘤變異性激性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。其他所有腫瘤的發生被認定是源自於該類動物自然發生的一般型腫瘤，與以fenotrol治療無生物學關連。BHEROTEC HFA及BHEROTEC CFC對呼吸道等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囊，顯示其耐受性佳。

包裝
100公播以下不鏽鋼罐裝
10公播定量噴霧液(=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：台灣百重佳股份有限公司
地址：台北市民生東路三段49/51號12樓
Composition
1 metered dose (puff) contains 1-(3,5-di-hydroxy-phenyl)-2-[1-(4-hydroxy-
benzoyl)-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 of the CFC-emulsion have been compared have shown the
formulations to be therapeutically equivalent.

Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively
stimulating beta_2-receptors in the therapeutic dose range. The stimulation of
beta_2-receptors comes into effect at a higher dose range. Occupation of beta_2-
receptors activates adenylyl cyclase via a stimulatory G_protein. The increase in
cyclase activity stimulates 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 phospholipid hydrolysis, and the
opening of large conductance calcium-activated potassium channels. There is
some evidence that the "max-K channel" can be directly activated via the G_
protein pathway.

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.

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, glycojenolysis,
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_1-receptor stimulation, and at supratherapeutic doses,
by beta_1-receptor stimulation. Tremor is more frequently observed effect of
beta_agonists. Unlike the effects on the bronchial smooth muscle, the
systemic effects of beta_agonists are subject to the development of tolerance.

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 therapeutic effect of BEROTEC is produced by a topical action in the
airways. 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 of BEROTEC are
can be considered equivalent.

Following inhalation of fenoterol hydrobromide in obstructive lung diseases,
bronchodilation 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 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 1\% of the dose has been determined.
Absorption then follows a biphasic course, 50\% of active hydrobromide being
rapidly absorbed with a half-life of 11 minutes, 70\% being slowly
absorbed with a half-life of 120 minutes.

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.

After oral administration, approximately 60\% of the fenoterol hydrobromide is
absorbed. The percentage, which has been absorbed, undergoes thorough
first-pass metabolism with the result that oral bioavailability falls to about
1.5\%. This is why the systemic drug effect of the active ingredients disappears
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_1/2 = 0.42 minutes, t_1/2 = 14.3 minutes
and t_1/2 = 3.2 hours. Metabolic transformation of fenoterol hydrobromide in
man occurs almost exclusively by sulfation, predominantly in the intestinal
wall.

In its non-metabolized 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.

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.
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.

(Fig. 1)

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. Hypersensitivity to fenoterol hydrobromide or inactive ingredients of the metered aerosol.

**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.

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, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma.
- In the case of acute, rapidly worsening dyspnoea (difficultly in breathing) a doctor should be consulted immediately.

Prolonged use:

On demand (symptom-oriented) treatment may be preferable to regular use. 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.

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of beta,-agonist containing drugs such as BEROTEC N 100 mcg/puff beyond the recommended dose over extended periods of time. The use of increasing amounts of beta,-agonist containing products like BEROTEC N 100 mcg/puff 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.

Potentially serious hypokalaemia may result from beta,-agonist therapy. 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, and xanthine derivatives (such as theophylline) 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.

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.

**Side Effects**

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,-agonist therapy. As with use of other inhalation therapy, cough, local irritation and less common, paradoxical bronchoconstriction have been reported.

As with other beta-mimetics, nausea, vomiting, sweating, weakness and myalgia/muscle cramps 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.

**Pregnancy and Lactation**

Pre-clinical data, 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.

Pre-clinical studies have shown that fenoterol is excreted into breastmilk. Safety during lactation has not been established.
Overdose

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 and flushing.

Therapy
Administration of sedatives, tranquilizers, in severe cases intensive therapy.

Beta-receptor blockers, preferably beta, 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.

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 and rabbits and in dogs between 150 and 433 mg/kg BW. Intravenous LD50 for mouse, rat, rabbit and dog was between 36 and 81 mg/kg BW. When administered by inhalation, toxicity was very low. Up to 670 mg/kg BW, 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, reduced glycogen content of muscle, reduced serum potassium levels (tachycardia)). At higher dosages, myocardial hypertrophy and/or lesions were observed in rat, mouse and rabbit at various administration routes from 1 mg/kg BW/d onwards, e.g. rabbits after i.v. administration over a period of 4 weeks. In the dog – most sensitive species to beta-adrenegics - these lesions were discerned from 0.019 mg/kg BW/d onwards.

Subacute inhalation studies in monkeys revealed no direct substance related toxic effects.

In reproduction toxicity studies, rats and rabbits revealed no teratogenic or embriotoxvxic effects, when administered by inhalation. Fertility and rearing were not impaired by fenoterol hydrobromide.

When administered perorally, doses up to 40 mg/kg BW/d had no deleterious effects on fertility of male and female rats. Daily oral doses up to 25 mg/kg BW in rabbits, and up to 38.5 mg/kg BW in mice showed neither embriotoxic nor teratogenic effects.

In rats toxicotic effects were observed at doses of 3.5 mg/kg BW/d, at 25 mg/kg BW/d, a slightly increased foetal and/or neonatal mortality occurred. Extremely high doses of 300 mg/kg BW/d p.o. and 20 mg/kg BW i.v. revealed an increased rate of malformations.

Mutagenic activity was not observed when fenoterol hydrobromide was treated in-vitro and in-vivo.

Carcinogenicity studies in mice (p.o., 18 months) and rats (p.o. and inhal., 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 and instillation of a 0.05 or 0.1 % solution into the conjunctival sac of rabbits were well tolerated.

Availability
Metered Aerosol

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

For
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