冠喘衛® 單一劑量吸入液
Combivent® Unit Dose Vials Inhalation Solution

Boehringer Ingelheim

衛署藥輸字第023357號

成分
每單一劑量吸入液(2.5 ml/瓶)含
(8r)-3a-hydroxy-8-isopropyl-1aH, 5aH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide monohydrate) 0.52 mg相當於
ipratropium bromide anhydrous 0.5 mg
Di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl) ethanol] sulphate (= salbutamol sulphate) 3.01 mg相當於salbutamol base 2.5 mg

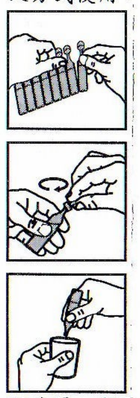
性質
Ipratropium bromide爲四級銨鹽化合物，具有抗乙醯膽鹼性質，能解除副交感神經作用(parasympatholytic)。臨床前的研究顯示ipratropium bromide能拮抗迷走神經所釋出之傳遞物質"乙醯膽鹼"(acetylcholine)的作用而抑制迷走神經所調節的反射作用。抗膽鹼激素藥物可抑阻乙醯膽鹼與位於支氣管平滑肌的毒蕈鹼性接受器(muscarinic receptor)作用，而抑制細胞內之環狀鳥糞嘌呤核苷單磷酸[cyclic guanosine monophosphate (即cyclic GMP)]濃度的增加。
Iprotropium bromide吸入後，其支氣管擴張作用主要是局部且特定作用於肺部而非全身。
Salbutamol sulphate爲一β_2擬交感神經劑(beta 2-adrenergic agent)，作用於呼吸道之平滑肌使其鬆弛。Salbutamol可鬆弛所有氣管及支氣管平滑肌，拮抗所有支氣管收縮而具保護作用。
COMBIVENT單一劑量吸入液含有ipratropium bromide及salbutamol，可以同時產生加成作用在肺部之毒蕈鹼接受體與b_2腎上腺素激性接受體(adrenergic receptor)上，使支氣管舒張，其作用比任何單一成分效果更好。對患有可逆性支氣管痙攣病患進行有對照組之研究，顯示COMBIVENT單一劑量吸入液之支氣管擴張療效大於其任一成分，但不會增加其不良反應。

藥物動力學
Ipratropium bromide經由口腔吸入可被迅速吸收，吸入後的全身生體利用率小於10%。靜脈注射ipratropium bromide約有46%的劑量會經腎臟排除，末相排除半衰期約爲1.6小時。放射線標定藥物所測之藥物及其代謝物的排除半衰期爲3.6小時。Iprotropium bromide無法穿透腦血管障壁。
Salbutamol sulphate經口吸入後無論是在氣道或吞入的部分均可迅速且完全地被吸收。最高血中濃度出現於投藥後3小時內，且投藥後24小時藥物以原型排於尿液中，排除半衰期爲4小時。
Salbutamol可穿透腦血管障壁，其濃度大約爲血漿濃度的5%。
Ipratropium bromide與salbutamol sulphate以噴霧機同時吸入，並不會增加個別的全身性吸收，而且COMBIVENT療效加成是因爲吸入後兩種主成分對肺部的局部作用相加所致。

適應症
用於治療阻塞性呼吸道疾病併發的可逆性支氣管痙攣需要一種以上支氣管擴張劑治療者。

用法用量
本藥須由醫師處方使用。
COMBIVENT單一劑量吸入液可經由適當的噴霧機或間歇性的正壓呼吸器給藥。
下列建議劑量適用於成人(包含老年人)及12歲以上的青少年：
治療急性發作
對大多數病人，一瓶單一劑量吸入液即可迅速緩解症狀。
情況嚴重的病人，若一瓶單一劑量吸入液無效，可能需要使用兩瓶單一劑量吸入液，但在這些情況，病患需立刻請教醫師或就近的醫院。
持續性治療
每次一瓶單一劑量，每日三至四次。

用法
單一劑量吸入液只可用適當噴霧機以吸入方式使用，不可口服或注射。



1. 根據醫師或製造廠指示，準備好噴霧機來充填藥品。
2. 下撕一個單一劑量瓶。
3. 用力旋轉頂部以打開單一劑量瓶。
4. 將單一劑量瓶的內容物擠入噴霧器的藥槽中。
5. 裝妥噴霧機，並依照指示使用。
6. 使用完畢後將藥槽中的殘留液體丟棄，依照指示清潔噴霧器。

因爲單一劑量瓶中不含有保存劑，所以打開後瓶中的內容物需很快用完。每次用藥均需使用新的小瓶，以避免被微生物感染。所以使用後剩餘部份、已開或單一劑量瓶已損壞者需丟棄。

絕不可將COMBIVENT吸入性溶液與其他藥物混合於同一噴霧機中。

禁忌
肥大阻塞性心肌病變、心律過速、對產品中任一成分或阿托品(atropine)及其衍生物過敏者禁用。

特別注意
使用COMBIVENT吸入液後可能立即發生過敏，如：蕁麻疹、血管性水腫、皮疹、支氣管痙攣以及口咽部水腫。
曾有個別案例報告，ipratropium bromide噴霧劑單獨使用或與一種腎上腺素β_2-作用劑合用時，若不慎進入眼睛，會發生眼部併發症，如：散瞳、眼內壓升高、窄角性青光眼、眼痛。
眼睛痛或不舒服、視力模糊、視界出現光暈或有色彩、伴隨因結膜充血而造成的紅眼、角膜水腫等可能是窄角性青光眼的症狀。若有任一項以上的上述症狀發生，應立即使用縮瞳劑治療並請教醫師。
必須指示病人正確地使用COMBIVENT單一劑量吸入液，並避免將COMBIVENT溶液或噴霧液噴入眼內。
建議噴霧溶液可經由含口器給藥，若沒有含口器，則可使用噴霧器的面罩。可能罹患青光眼的病患使用時，須特別告知其注意保護眼睛。
COMBIVENT使用於下列情況下，且劑量超過推薦劑量時，應謹慎評估其使用益處勝過危險時，方得使用：
未完全控制病情之糖尿病、最近患有心肌梗塞、嚴重心臟或血管病變、甲狀腺機能亢進、親鉻細胞瘤、可能罹患窄角性青光眼、前列腺肥大或膀胱頸阻塞。
從一些上市後的資料及發表的文獻證據顯示salbutamol與引起心肌缺血有關，但相當罕見。對於正接受salbutamol治療呼吸道疾病又合併嚴重心臟疾病(例如：缺血性心臟病、心搏過速或嚴重的心臟衰竭)的病人，須告知若出現胸痛，或心臟病惡化的其他症狀，應尋求醫師的建議。
β_2-作用劑可能會造成嚴重的低血鉀症
此外，缺氧會使低血鉀症惡化。
纖維囊腫的病人可能更容易發生胃腸道蠕動障礙。
若患者發生急性且繼續惡化的呼吸困難時，應立即請教醫師。
若病人需要持續使用高於推薦劑量的劑量來控制症狀，則應檢討病人的治療計畫。

藥物交互作用
同時使用b-擬交感神經劑、黃嘌呤衍生物及抗乙醯膽鹼類藥物可能增加COMBIVENT的副作用。
β-擬交感神經作用劑(beta-adrenergic agonists)所引發之低血鉀症機率會因併用黃嘌呤衍生物、皮質類固醇及利尿劑而增加，尤其是患有嚴重的呼吸道阻塞患者應特別注意。
低血鉀症會造成使用digoxin之患者易發作心律不整。
這種情況下，建議監測患者血漿中鉀離子的濃度。
與β-阻斷劑併用時可能會大幅降低支氣管擴張的效果。
單胺氧化抑制劑(monoamine oxidase inhibitor)及三環抗鬱藥會使β-擬交感神經作用劑的作用增強，併用時須小心。
含鹵素原子的吸入性碳氫麻醉劑，如：halothane、trichloroethylene及enflurane會加強β-作用劑的心血管作用。

懷孕與哺乳
懷孕期間使用COMBIVENT的安全性尚未建立。通常懷孕期間用藥需加以觀察，尤其是懷孕第一期。應注意
COMBIVENT會抑制子宮收縮。
Salbutamol sulphate與ipratropium bromide可能分泌至乳汁中，其對新生兒的影響仍然未知。雖然脂不溶性的四級鹼基可進入乳汁中，但ipratropium bromide不可能在嬰兒體內到達有意義的限度，尤其是以吸入方式給藥。由於很多藥物都可以出現在分泌之乳汁中，因此當哺乳婦女使用COMBIVENT時，仍須加以提醒。

副作用
免疫系統障礙：
過敏性反應
過敏性反應過度
代謝及營養障礙：
低鉀血症
精神障礙：
精神障礙
精神緊張
神經系統障礙：
眩暈
頭痛
震顫
眼睛障礙：
窄角性青光眼
眼痛
眼內壓上升
散瞳
視力模糊
Ipratropium bromide噴霧劑，單方或與β_2-交感神經興奮劑合併的複方，若不慎噴入眼睛，都曾有病例發生眼睛併發症。
心臟障礙：
心律不整
心房纖維顫動
心肌缺血
心悸
心跳過快
舒張壓降低
收縮壓上升
呼吸、胸及縱膈障礙：
支氣管痙攣
喉痙攣
咽部水腫
咳嗽
發聲困難
咽喉刺激感
胃腸障礙：
嘴水腫
口乾
胃腸道運動障礙
噁心
嘔吐
皮膚及皮下組織障礙：
血管性水腫
多汗
發疹
皮膚反應
蕁麻疹
骨骼肌肉及結締組織障礙：
肌肉痙攣
肌肉無力
肌痛
腎臟及泌尿障礙：
尿滯留
一般障礙及投與部位的狀況：
無力

過量
症狀
過量主要與salbutamol有關。
過量時所產生的症狀即爲β-擬交感神經刺激過度時的症狀，最常見的有心跳過速、心悸、震顫、高血壓、低血壓、脈壓變寬、心絞痛、心律不整與發熱。
Ipratropium bromide過量時的症狀有口乾、視力調節障礙等，由於其治療劑量範圍寬，且只有局部使用，因此其症狀輕微且短暫。
治療
對嚴重者給予鎮靜劑與安神劑。
β-受體阻斷劑，特別是選擇性β_1受體阻斷劑，適合爲特定的解毒劑，但需考慮其可能增加支氣管阻塞，所以對支氣管氣喘病患，劑量需小心調整。

毒物學
對大鼠與狗投與單一吸入劑量的COMBIVENT觀察其急性毒性，技術上所能投與的最高劑量(ipratropium bromide/salbutamol)大鼠爲887/5397μg/kg bw，狗165/862μg/kg bw，在此最高劑量下並無全身性毒性，且局部耐受性良好。半數致死量(LD_{50})的計算乃依ipratropium bromide測試動物的種類選擇劑量，分別靜脈注射12 ~ 20 mg/kg bw之ipratropium bromide與60 ~ 70 mg/kg之salbutamol。
有兩個爲期13週，針對大鼠及狗測試ipratropium bromide與salbutamol併用時其吸入毒性的研究顯示心臟爲標的器官。給予大鼠ipratropium bromide/salbutamol劑量範圍爲31.3/183.4 ~ 375.5/2188.4μg/kg bw/day時，可觀察到心臟的重量增加，但與劑量無關，且沒有任何可測得的病理變化。狗的投與劑量則爲ipratropium bromide/salbutamol 32.3/197.5 ~ 129.2/790.4μg/kg bw/day，其心跳速率稍微增加，劑量較高時，可觀察到左心室乳頭肌出現瘢痕及/或纖維化，有時會伴隨有礦質化。
上述試驗中的發現皆爲β-擬交感神經劑，(如salbutamol)的已知作用。
第二個成分ipratropium bromide的毒性也熟知多年，爲典型的抗乙醯膽鹼的作用，如：黏膜乾燥、散瞳，在狗則會出現乾性角膜結膜炎(乾眼)，並會減少大鼠胃腸道之張力及抑制胃腸道蠕動。
曾對COMBIVENT個別的主成分研究其生殖毒性，高劑量的salbutamol會造成小鼠裂顎畸形，這種情形也出現於投與其他β-擬交感神經興奮劑之後，或被認爲由於全身性壓力引起母體的皮質脂酮(corticosterone)濃度上升，與其他動物物種無關。此外，根據臨床前試驗的發現，salbutamol被懷疑有致畸胎的可能性，故婦女使用時要特別注意。除了上述的發現，這些針對salbutamol及ipratropium bromide所做的研究得到的結果不論是對胚胎、胎兒或年幼的哺乳動物，都屬於母體毒性的範圍。
體內與體外試驗均顯示salbutamole與ipratropoium bromide沒有致突變性。
Salbutamol與ipratropium bromide分別作過數個體內致癌性研究。
當小鼠口服salbutamol劑量爲人類吸入劑量的100倍以上時，其卵巢系膜出現平滑肌瘤的機會增加，但此情形未見於大鼠與狗。若同時服用β-拮抗劑可防止平滑肌瘤的生成。上述情形只和生物種類有關，且無臨床相關性，因此，salbutamol的臨床使用並不受限制。
小鼠與大鼠口服ipratropium bromide並無致腫瘤性。
沒有證據顯示COMBIVENT與其個別活性成分會造成免疫毒性。

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Combivent® Unit Dose Vials

Boehringer Ingelheim

Composition

1 unit-dose vial (2.5 ml) solution for inhalation contains:
(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate 0.52 mg (= ipratropium bromide) corresponding to 0.5 mg ipratropium bromide anhydrous
di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanol] sulphate (= salbutamol sulphate) corresponding to 2.5 mg salbutamol base 3.01 mg

Properties

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature. Salbutamol sulphate is a $beta_2$-adrenergic agent which acts on airway smooth muscle resulting in relaxation.
Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against all bronchoconstrictor challenges.
COMBIVENT unit dose vials provide the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the additive effect on both muscarinic and $beta_2$-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent. Controlled studies in patients with reversible bronchospasm have demonstrated that COMBIVENT unit dose vials have a greater bronchodilator effect than either of its components and there was no potentiation of adverse events.

Pharmacokinetics

Ipratropium bromide is quickly absorbed after oral inhalation. The systemic bioavailability after inhalation is estimated to be less than 10% of the dose. Renal excretion of ipratropium bromide is given as 46% of the dose after intravenous administration. The half-life of the terminal elimination phase is about 1.6 hours as determined after intravenous administration. The half-life for elimination of drug and metabolites is 3.6 hours, as determined after radio labeling. Ipratropium bromide does not penetrate the blood brain barrier. Salbutamol sulphate is rapidly and completely absorbed following oral adminstration either by the inhaled or gastric route. Peak plasma salbutamol concentrations are seen within three hours of administration and is excreted unchanged in the urine after 24 hours. The elimination half-life is 4 hours. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about five percent of the plasma concentrations. It has been shown that co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and that therefore the additive activity of COMBIVENT unit dose vials is due to the combined local effect on the lung following inhalation.

Indications

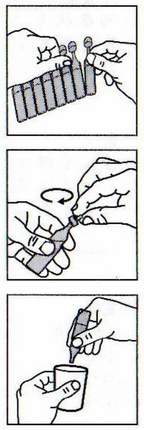
COMBIVENT unit dose vials are indicated for the management of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

Dosage and Administration

The product should be used by physician prescription
COMBIVENT inhalation solution in unit dose vials may be administered from a suitable nebuliser or an intermittent positive pressure ventilator. The following dose is recommended for adults (including elderly patients) and adolescents over 12 years of age:
Treatment of acute attacks:
1 unit dose vial is sufficient for prompt symptom relief in many cases. In severe cases if an attack has not been relieved by one unit dose vial, two unit dose vials may be required. In these cases, patients should consult the doctor or the nearest hospital immediately.
Maintenance treatment:
1 unit dose vial three or four times daily.

Instructions for use

The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.



1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or doctor.
2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the content of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.
It is strongly recommended not to mix COMBIVENT solution for inhalation with other drugs in the same nebuliser.

Contraindications

Hypertrophic obstructive cardiomyopathy, tachyarrhythmia. Hypersensitivity to any of the components of the product, to atropine or its derivatives.

Special Precautions

Immediate hypersensitivity reactions may occur after administration of COMBIVENT solution for inhalation, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has escaped into the eyes.
Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately. Patients must be instructed in the correct administration of COMBIVENT unit dose vials. Care must be taken not to expose the eyes to the solution or aerosol of COMBIVENT. It is recommended that the nebulised solution be administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes. In the following conditions COMBIVENT 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, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g.ischaemic heart disease, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances. In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately. If higher than recommended doses of COMBIVENT are required to control symptoms, the patients's therapy plan should be reviewed by a doctor.

Drug Interactions

The concurrent administration of xanthine derivatives as well as other beta-adrenergics and anticholinergics may increase the side effects. Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction. 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. A potentially serious reduction in bronchodilator effect 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.

Pregnancy and Lactation

The safety of COMBIVENT during human pregnancy is not established. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed. The inhibitory effect of COMBIVENT on uterine contraction should be taken into account. Salbutamol sulphate and ipratropium bromide are probably excreted in breast milk and their effects on the neonate are not known. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when COMBIVENT is administered to a nursing woman.

Side Effects

Immune system disorders:
Anaphylactic reaction
Hypersensitivity
Metabolism and nutrition disorders:
Hypokalaemia
Psychiatric disorders:
Mental disorder
Nervousness
Nervous system disorders:
Dizziness
Headache
Tremor
Eye disorders:
Angle closure glaucoma
Eye pain
Intraocular pressure increased
Mydriasis
Vision blurred
There have been isolated reports of ocular complications with symptoms mentioned above when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has escaped into the eyes.
Cardiac disorders:
Arrhythmia
Atrial fibrillation
Myocardial ischaemia
Palpitations
Tachycardia
Blood pressure diastolic decreased
Blood pressure systolic increased
Respiratory, thoracic and mediastinal disorders:
Bronchospasm
Laryngospasm
Pharyngeal oedema
Cough
Dysphonia
Throat irritation
Gastrointestinal disorders:
Oedema mouth
Dry mouth
Gastrointestinal motility disorder
Nausea
Vomiting
Skin and subcutaneous tissue disorders:
Angioedema
Hyperhidrosis
Rash
Skin reaction
Urticaria
Musculoskeletal and connective tissue disorders
Muscle spasms
Muscular weakness
Myalgia
Renal and urinary disorders:
Urinary retention
General disorders and administration site conditions:
Asthenia

Overdosage

Symptoms
The effects of overdosage are expected to be primarily related to salbutamol. 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. Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accomodation disturbances) are mild and transient in nature in view of the wide therapeutic range and topical administration.
Therapy
Administration of sedatives, tranquillizers, 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

The acute toxicity of COMBIVENT after single inhalation administration was tested in rats and dogs. Up to the highest technically testable dose (rat: 887/5397 µg/kg bw [ipratropium bromide/salbutamol], dog: 165/862 µg/kg bw [ipratropium bromide/salbutamol]) there were no indications of systemic toxic effects, the compound was locally well tolerated. The approximate LD50 after intravenous administration was calculated for the single substances to be between 12 and 20 mg/kg bw for ipratropium bromide and between 60 and 70 mg/kg for salbutamol depending on the tested species ipratropium bromide (mouse, rat, dog). Two 13 week inhalation toxicity studies in rats and dogs, respectively, have been performed with the combination of ipratropium bromide and salbutamol. In these studies, the heart proved to be the target organ. At doses of 31.3/183.4 to 375.5/2188.4 µg/kg bw/day ipratropium bromide/salbutamol, in the rat a not dose dependent increase in heart weights was observed, however without any histopathological detectable changes.
In the dog at doses of 32.3/197.6 to 129.2/790.4 µg/kg bw/day ipratropium bromide/salbutamol, slightly increased heart rates and, at the higher dosages, histopathologically detectable scars and/or fibrosis in the papillary muscle of the left ventricle, sometimes accompanied with mineralisation, were observed. The findings obtained in the above mentioned studies must be regarded as well known effects of β-adrenergics as salbutamol. The toxicological profile of the second component (ipratropium bromide) is also well known for many years and characterised by typical anticholinergic effects as dryness of the mucosal membranes of the head, mydriasis, keratoconjunctivitis sicca (dry eye) in dogs only, reduction in tone and inhibition of motility in the gastrointestinal tract (rat). Reproduction toxicity studies are available for the two individual components of COMBIVENT. Salbutamol caused cleft palates at high doses in mice. This phenomenon is well known and occurs also after the administration of other beta-adrenergic compounds. Today it is assumed that this effect is caused by an increase in the maternal corticosterone level and might be regarded as a result of general stress not relevant for other species. Additionally, the preclinical findings which gave rise to the suspicion that salbutamol could have teratogenic properties have already been taken into account by the restriction concerning the use in women. Apart from these findings, the studies performed with salbutamol and with ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity. Both individual substances were tested in numerous in-vivo and in-vitro tests. Neither salbutamol nor ipratropium bromide showed any evidence of mutagenic properties.
Salbutamol and ipratropium bromide were tested separately for neoplastic properties in several in vivo carcinogenicity studies. After oral administration of salbutamol in mice, but not in rats and dogs, an increased incidence of leiomyomas of the mesovarium was observed at doses more than 100 times higher than the human inhalation dose. The development of the leiomyomas was found to be preventable by simultaneous administration of beta-blockers. These findings were assessed to be species specific and without clinical relevance, consequently not leading to any restriction of the clinical use of salbutamol. Ipratropium bromide revealed no carcinogenic potential when tested orally in mice and rats. No evidence was found of any immunotoxicological effect caused by COMBIVENT or its single active ingredients.

Availability

Solution for inhalation in unit dose vials: below 100 unit dose vials in paper box

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

MFD. BY
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