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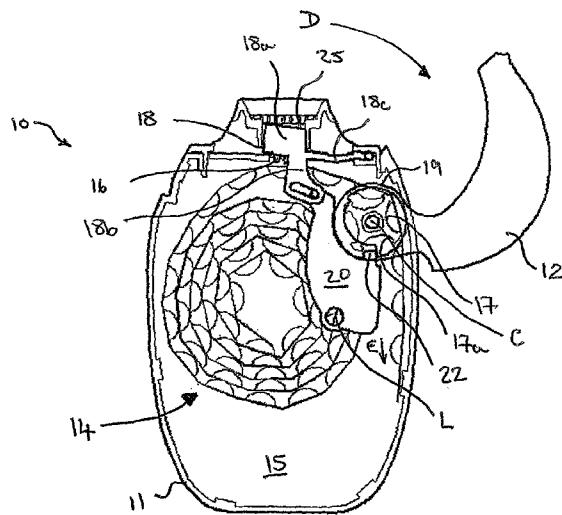


Figure 4

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(57) Abstract: An inhaler (10) comprising a housing (11) to receive a strip (14) having a plurality of blisters (14a), each blister (14a) having a puncturable lid (14c) and containing a dose of medicament for inhalation by a user, a mouthpiece (13) through which a dose of medicament is inhaled by a user, a cap (12) to cover the mouthpiece (13) and a blister piercing element (16) to pierce the lid (14c) of a blister (14a) is disclosed. The cap (12) is rotatable to drive the strip (14) to sequentially move each blister (14a) into alignment with the blister piercing element (16) and an actuator is operable in response to rotation of the cap (12) to cause the blister piercing element (16) to puncture the lid (14c) of an aligned blister (14a) such that, when a user inhales through the mouthpiece (13), an airflow through the blister (14a) is generated to entrain the dose contained therein and carry it out of the blister (14a) and via the mouthpiece into the user's airway.



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## Inhaler

### Description

The present invention relates to an inhalation device for oral or nasal delivery of medicament in powdered form. More specifically, the invention relates to an inhaler having a housing to receive a strip having a plurality of blisters spaced along the length of the strip, each blister having a puncturable lid and containing a dose of medicament for inhalation by a user. The invention also relates to an inhaler containing a strip of blisters each having a puncturable lid and containing a dose of medicament for inhalation by a user of the device according to the invention.

Oral or nasal delivery of a medicament using an inhalation device is a particularly attractive method of drug administration as these devices are relatively easy for a patient to use discreetly and in public. As well as delivering medicament to treat local diseases of the airway and other respiratory problems, they have more recently also been used to deliver drugs to the bloodstream via the lungs, thereby avoiding the need for hypodermic injections.

It is common for dry powder formulations to be pre-packaged in individual doses, usually in the form of capsules or blisters which each contain a single dose of the powder which has been accurately and consistently measured. A blister is generally cold formed from a ductile foil laminate or a plastics material and includes a puncturable lid which is permanently heat-sealed around the periphery of the blister during manufacture and after the dose has been introduced into the blister. A foil blister is preferred over capsules as each dose is protected from the ingress of water and penetration of gases such as oxygen in addition to being shielded from light and UV radiation all of which can have a detrimental effect on the delivery characteristics of the inhaler if a dose becomes exposed to them. Therefore, a blister offers excellent environmental protection to each individual drug dose.

Inhalation devices that receive a blister pack comprising a number of blisters each of which contain a pre-metered and individually packaged dose of the drug to be delivered are known. Actuation of the device causes a mechanism to breach or rupture a blister, such as by puncturing it or peeling the lid off, so that when 5 the patient inhales, air is drawn through the blister entraining the dose therein that is then carried out of the blister through the device and via the patient's airway down into the lungs. Pressurized air or gas or other propellants may also be used to carry the dose out of the blister. Alternatively, the mechanism that punctures or opens the blister may push or eject the dose out of the blister into a 10 receptacle from which the dose may subsequently be inhaled.

It is advantageous for the inhaler to be capable of holding a number of doses to enable it to be used repeatedly over a period of time without the requirement to open and/or insert a blister into the device each time it is used. Therefore, many 15 conventional devices include means for storing a number of blisters each containing an individual dose of medicament. When a dose is to be inhaled, an indexing mechanism moves a previously emptied blister away from the opening mechanism so that a fresh one is moved into a position ready to be opened for inhalation of its contents.

20 An inhaler of the type described above is known from the Applicant's own co-pending international application no. PCT/GB2004/004416 filed on 18<sup>th</sup> October 2004 and claiming priority from GB0324358.1 filed 17<sup>th</sup> October 2003. This international application has been published as WO2005/037353 A1.

25 According to one embodiment described and claimed in WO 2005/037353 A1, and illustrated in Figures 1a and 1b of the accompanying drawings, an inhaler 1 has a housing 2 containing a coiled strip of blisters 3. An indexing mechanism 4 comprising a single actuating lever 5 unwinds the coil 3 one blister at a time so 30 that they pass over a blister locator chassis 6 and successively through a blister piercing station 7, when the actuator 5 is pivoted in a direction indicated by arrow "A" in Figure 2. The blister 3a located at the blister piercing station 7 on

each movement of the actuator 5 is pierced on the return stroke of the actuator 5 (in the direction indicated by arrow "B" in Figure 2) by piercing elements 8 on the actuator 5 itself so that, when a user inhales through a mouthpiece 9, an airflow is generated within the blister 3a to entrain the dose contained therein 5 and carry it out of the blister 3a via the mouthpiece 9 and into the user's airway.

In another embodiment disclosed in WO2005/037353 A1, indexing and piercing of a blister positioned at the blister piercing station 7 is carried out in response to rotation of the cap rather than as a result of direct rotation of the actuator by 10 the user.

The present invention seeks to provide further improved embodiments of inhalation device of the type disclosed in WO2005/037353 A1, that has a relatively simple construction, is robust, straightforward to manufacture and easy 15 for the patient to use.

According to the invention, there is provided an inhaler comprising a housing to receive a strip having a plurality of blisters, each blister having a puncturable lid and containing a dose of medicament for inhalation by a user, a mouthpiece 20 through which a dose of medicament is inhaled by a user, a cap to cover the mouthpiece and, a blister piercing element to pierce the lid of an aligned blister, the cap being rotatable to drive the strip to sequentially move each blister into alignment with the blister piercing element and, an actuator operable in response to rotation of the cap to cause the blister piercing element to puncture the lid of 25 an aligned blister such that, when a user inhales through the mouthpiece, an airflow through the blister is generated to entrain the dose contained therein and carry it out of the blister and via the mouthpiece into the user's airway.

In a preferred embodiment, the actuator is pivotally mounted to the housing 30 such that it rotates in response to rotation of the cap to cause the blister piercing element to pierce the lid of an aligned blister.

In one embodiment, the inhaler preferably comprises a link arm that couples the cap to the actuator to rotate the actuator in response to rotation of the cap. The link arm may be pivotally mounted to the housing.

5 The link arm is preferably coupled to the actuator so that the actuator rotates relative to the housing to draw the blister piercing element into the lid of an aligned blister when the link arm rotates.

10 The inhaler preferably includes cooperating cam elements on the actuator and on the link arm such that rotation of the link arm causes rotation of the actuator to draw the blister piercing element into the lid of an aligned blister. However, in an alternative embodiment, the inhaler includes a compliant linking member coupling the link arm to the actuator. The compliant linking member may be formed from a resilient strip that is configured to deform in response to the 15 application of a force thereto which is greater than the force required to pivot the actuator into a piercing position.

20 In one embodiment, the cooperating cam elements comprise a cam follower on the link arm and a cam guide on the actuator, the cam follower and cam guide being configured such that the cam follower follows the cam guide when the link arm rotates to rotate the actuator.

25 The cam guide may comprise a slot in the actuator and the cam follower may comprise a pin on the link arm slideably received in the slot.

30 The link arm can be a plate and the actuator may include a leg extending into the housing. In one embodiment, the plate and leg may have a region of overlap so that the pin upstands from the plate and is received in the slot in said region of overlap.

35 The inhaler preferably comprises a link arm drive element rotatable together with the cap, the drive element and link arm being configured such that they

cooperate with each other for part of the rotation of the cap so that the link arm rotates when the user rotates the cap, although in one embodiment, the link arm drive element may be drive features formed within, and preferably integrally with, the cap.

5

The drive element and link arm are preferably configured such that they cooperate when the cap has almost reached its open position so that further rotation of the cap into the open position rotates the link arm.

10 Advantageously, the drive element and link arm are configured such that they cooperate when the cap has almost reached its closed position so that further rotation of the cap into its closed position rotates the link arm in the opposite direction back to its original position.

15 The link arm drive element may comprise a first shoulder that engages the link arm to rotate the link arm when the cap is rotated from its closed to its open position and, a second shoulder that engages the link arm to rotate the link arm in the opposite direction when the cap is rotated from its open to its closed position.

20

In a particular embodiment, the drive element comprises a disc-shaped member.

The drive element can be integral with the cap.

25 The disc may have an arcuate recess extending around a portion of its circumference and the first and second shoulders can be defined by radially extending walls at each end of the arcuate recess.

30 In one embodiment, the link arm preferably includes a tooth, the tooth being received within the arcuate recess in the disc such that the first shoulder contacts the tooth as the cap is rotated from its closed to its almost fully open position so that further rotation of the cap causes the first shoulder to push against the

tooth to rotate the link arm and, such that the second shoulder contacts the tooth as the cap is rotated from its open to its almost closed position so that further rotation of the cap causes the second shoulder to push against the tooth to rotate the link arm in the opposite direction.

5

In another embodiment, the cap includes a profiled cam guide and the actuator includes a cam follower that follows the profile of the cam guide during rotation of the cap.

10 The profiled cam guide may be configured such that, as the cap is rotated, the cam follower follows the profile so as to move the actuator into a raised position.

15 In a most preferred embodiment, the profiled cam guide is configured such that the cam follower follows the profile so as to move the actuator into said raised position during rotation of the cap from its open position to its closed position.

20 In an alternative embodiment, the profiled cam guide may be configured such that the cam follower follows the profile so as to move the actuator into said raised position during rotation of the cap from its closed position to its open position.

25 In some embodiments, a portion of the cam guide has a curved surface and the cam follower follows said portion as the cap is rotated from its closed into its open position. Preferably, the actuator is in a raised position when the cap is closed and remains substantially stationary as the cam follower follows said curved surface of the cam guide during opening of the cap.

30 The inhaler may include a torsion spring and a mechanism to tension the torsion spring in response to rotation of the cap from its closed into its open position.

Such a mechanism can include a toothed gear mounted for rotation together with the cap and a driven gear pivotally mounted to the housing and lying in meshing engagement with the toothed gear.

- 5 If a torsion spring is used, it may comprise an arm cooperatively engaged with the driven gear such that, when the driven gear rotates during opening of the cap, the arm is deflected to tension the torsion spring and bias the actuator assembly in a blister piercing direction.
- 10 In yet another alternative embodiment, the profiled cam guide can be configured such that the cam follower follows the profile so as to move the actuator from an initial position into an intermediate position, between the initial position and raised position, during rotation of the cap from its open to its closed positions and, to move the actuator from said intermediate position to said raised position during rotation of the cap from its closed to its open positions.
- 15

The alternative arrangements in which the actuator is raised during opening of the cap have the additional advantage that the space within the cap does not have to be large enough to contain the actuator in its fully raised position which is necessary when the actuator is raised completely during closure of the cap. On the contrary, the space within the cap only has to be sufficient to contain the actuator in its intermediate position as the raised position is only reached as the cap is opened on a subsequent stroke.

25

Conveniently, the profiled cam guide can be integral with the cap. However, the profiled cam guide can also be a separate element which is associated with the cap and configured to move together with the cap.

- 30 The inhaler may include biasing means associated with the actuator such that the actuator moves from its initial position into its raised position against a biasing

force provided by the biasing means that biases the actuator towards its initial position.

In this embodiment, the curved surface ends when the cap reaches its open 5 position and the cam follower falls off the end of the curved surface to enable the biasing force to rotate the actuator so that the blister piercing element pierces the lid of an aligned blister.

In one embodiment, the cam guide comprises two cam guide portions and the 10 return path is defined by a channel between the two cam guide portions.

The cam follower may comprise a pin extending from the actuator. The actuator may also comprise a leg extending into the housing with the cam follower upstanding from a free end of the leg.

15 In a preferred embodiment, the biasing means comprises a spring extending between the actuator and the housing.

In one embodiment, the mouthpiece is formed integrally with the actuator. 20 Alternatively, the actuator is attached to the mouthpiece such that the mouthpiece and actuator rotate together. Alternatively, the actuator rotates independently of the mouthpiece.(for either principal embodiment).

25 In any embodiment of the invention, the mouthpiece and actuator may be integrated so as to form a mouthpiece/actuator unit, the mouthpiece/actuator unit being operable in response to rotation of the cap to cause the blister piercing element to puncture the lid of an aligned blister such that, when a user inhales through the mouthpiece, an airflow through the blister is generated to entrain the dose contained therein and carry it out of the blister and via the 30 mouthpiece into the user's airway.

Preferably, the mouthpiece/actuator unit comprises an actuator portion and a mouthpiece portion attached to each other. Alternatively, the mouthpiece/actuator unit can be formed or moulded as a single component.

5 If the mouthpiece portion and actuator portion are separate components, they may be separable from each other.

Advantageously, the mouthpiece/actuator unit includes a flow path for the flow of medicament through the mouthpiece/actuator unit into the patient's airway.

10

In one embodiment, the blister piercing element comprises an insert, said insert being located within the flow path in the mouthpiece actuator unit, said insert having openings therein for the passage of medicament therethrough. The blister piercing elements conveniently depend from said insert mounted in the flow path.

15

In other embodiments, the actuator and mouthpiece can be formed as separate components and the mouthpiece can be immovably attached to the housing. In this case, the actuator is mounted for rotation relative to the mouthpiece and to the housing.

20

When the actuator is mounted for rotation, it may include a pivot arm, a free end of the pivot arm being pivotally mounted to the housing. In one embodiment, the free end of the pivot arm may be captured between the mouthpiece and the housing to pivotally mount the end of the pivot arm.

25 The mouthpiece preferably includes a flow path for the flow of air and medicament from a punctured blister through the mouthpiece into the patient's airway. A portion of the actuator can be movably received within the flow path in the mouthpiece, said portion having passages therethrough for the flow of air and medicament through said portion. The blister piercing elements can depend from said portion of the actuator mounted in the flow path of the mouthpiece.

In any embodiment of the invention, the inhaler may comprise an indexing mechanism to sequentially move each blister into alignment with the blister piercing element.

5

In a preferred embodiment, the indexing mechanism comprises a drive member that engages the blister strip to drive the strip to sequentially move each blister into alignment with the blister piercing element.

10 The cap and drive member are preferably configured such that the cap and drive member cooperate on rotation of the cap from a closed position, in which the cap covers the mouthpiece, towards an open position, in which the mouthpiece is exposed for inhalation through the mouthpiece, so that the drive member drives the strip and moves a blister into alignment with the blister piercing element.

15

20 The cap and drive member are preferably configured such that the cap is de-coupled from the drive member as the cap reaches its fully open position, so that there is no drive to the strip as the cap is rotated in the opposite direction from its open position back to its closed position.

25 In a more preferable embodiment, the cap and drive member are configured such that the cap is de-coupled from the drive member before the cap reaches its open position so that there is no drive to a strip as the cap is rotated further in the same direction towards its fully open position. In connection with the first embodiment of the invention, this has the advantage that a blister has been aligned with the blister piercing member and movement of the blister strip has stopped prior to piercing of said aligned blister.

30 It will be appreciated that it is advantageous that the decoupling of the cap and drive member takes place when the cap has reached or has almost reached the open position so that a user can partially open the cap to clean and/or inspect

the mouthpiece and close it again without indexing a blister. The return or abort stroke in this case will then cause the strip to move back to its original position as it was prior to movement of the cap, as long as the point at which the cap and drive member become de-coupled has not been reached prior to movement of 5 the cap back towards its closed position.

In one embodiment, the drive member comprises a wheel, the cap and the drive wheel both being mounted to the housing for rotation about the same axis.

10 According to another aspect, there is provided an inhaler according to the invention containing a strip of blisters each having a puncturable lid and containing a dose of medicament for inhalation by a user.

Embodiments of the invention will now be described, by way of example only, 15 with reference to Figures 3 to 8 of the accompanying drawings, in which:  
FIGURE 1 and 2 are side views of a conventional inhalation device to show how a strip is driven to sequentially move blisters into alignment with a blister piercing element by movement of an actuator from the position shown in Figure 1 to the position shown in Figure 2 which drives an indexing wheel. A piercing head on the actuator pierces the lid of an aligned blister when the actuator is 20 returned to its normal position, as shown in Figure 1;  
FIGURE 3a is a side view of an inhalation device according to a first embodiment of the present invention with the cap in its closed position covering the mouthpiece;  
25 FIGURE 3b is an enlarged partial view of the inhalation device shown in Figure 3a;  
FIGURE 4 is a side view of the inhalation device shown in Figure 1 following rotation of the cap from its closed position to a position just prior to its fully open position;  
30 FIGURE 5 is a side view of the inhalation device shown in Figure 3 and 4 following rotation of the cap from the position shown in Figure 4 to a fully open position;

FIGURE 6a is a side view of an inhalation device according to a second embodiment of the invention with the cap in its closed position covering the mouthpiece;

FIGURE 6b is an enlarged partial view of the inhalation device shown in Figure 5 6a;

FIGURE 7 is a side view of the inhalation device shown in Figure 6 following rotation of the cap from its closed position to its fully open position but before any movement of the actuator has taken place;

FIGURE 8 is a side view of the inhalation device shown in Figures 6 and 7 after 10 the actuator has dropped to cause the blister piercing member to pierce the lid of an aligned blister;

FIGURE 9 is a partial perspective view of an inhaler incorporating an improved 15 blister strip indexing mechanism which can be used in the inhaler of the embodiments of the invention, with the actuator in its home or stowed position prior to use of the inhaler;

FIGURE 10 is a partial perspective view of the inhaler shown in Figure 9 in which the actuator has been rotated into an intermediate position from its home position;

FIGURE 11 is the same view as shown in Figure 10, but with the cantilevered 20 chassis arm omitted for clarity;

FIGURE 12 is a partial perspective view of the inhaler shown in Figures 9 to 11, after the actuator has been rotated to a point at which drive between the drive coupling and the actuator has disengaged;

FIGURE 13 is a partial perspective view of the opposite side of the inhaler 25 shown in Figures 9 to 12;

FIGURE 14a is a perspective view of the drive coupling used in the indexing mechanism of the inhaler shown in Figures 9 to 13;

FIGURE 14b is a side view of the drive coupling illustrated in Figure 14a in which the flexible flange portion has been deflected in a direction "T" towards 30 the shaft or, towards an indexing wheel mounted on that shaft;

FIGURE 15a to 15c show a modified version of the embodiment described with reference to Figures 3 to 5 which employs a compliant linkage rather than a cam assembly;

FIGURE 16a to 16e shows a modified version of the embodiment described with reference to Figures 6 to 8 which employs a torsion spring and gear mechanism; and

FIGURES 17a to 17f show another embodiment of inhalation device according to the present invention that has a cam guide and latch mechanism.

10 Referring now to the first embodiment illustrated in Figures 3a to 5 of the accompanying drawings, there is shown an inhaler 10 having a housing 11, a cap 12 pivotally mounted to the housing 11 for rotation about an axis marked "C" from a closed position, as shown in Figure 3a and 3b in which the cap 12 covers and protects a mouthpiece 13 to a fully open position, as shown in Figure 5 and indicated by arrow "D", in which the mouthpiece 13 is exposed to enable a user to inhale a dose of medicament through the mouthpiece 13.

For clarity, the inhalation device 10 of the invention is shown with a portion of its housing 11 removed so that its internal workings and components are visible.

20 The components are also visible through the cap 12, although the cap 12 may be opaque in the actual device.

A strip 14 having a plurality of individually spaced moisture proof blisters 14a each containing a pre-measured dose of powdered medicament for inhalation is coiled up within the housing 11. Each blister 14a of the strip 14 comprises a generally hemispherically shaped pocket 14b and a flat puncturable lid 14c permanently heat sealed to the pocket 14b to hermetically seal the dose therein. The strip 14 is preferably manufactured from foil laminate or a combination of foil laminate, such as aluminium, and plastics material.

30

Although a region 15 is provided within the housing 11 to receive the used portion 14d of the strip 14, it will be appreciated that the invention is also

applicable to other inhalation devices (not shown) in which used blisters 14d are not retained within the housing 11 but pass out through an opening (not shown) in the wall of the housing 11 for periodic detachment by a user.

5 The inhaler 10 includes an indexing mechanism to index the strip 14, i.e. to sequentially move each blister 14b forward by a sufficient distance on each rotation of the cap 12 so as to move a fresh blister 14b into alignment with a blister piercing element 16 which is operable to puncture the lid of an aligned blister 14b to facilitate access to the dose contained therein. Although reference 10 is made to a blister piercing element 16, it will be appreciated that multiple openings are formed in the lid 14c of the blister 14b so that air can be drawn into the blister 14b through one or some of those openings and flow out of the blister 14b, together with an entrained dose of medicament, through one or more other openings.

15

The indexing mechanism comprises a drive wheel 17 coaxially mounted for rotation along the same axis "C" as the cap. The drive wheel 17 has four spokes 17a. As can be seen in Figure 3a and 3b, the strip 14 passes around the drive wheel 17 and individual blisters 14a are held between the spokes 17a. As the 20 drive wheel 17 rotates (in a clockwise direction as shown in the drawings), the strip 14 is indexed forward, in a direction indicated by arrow "E".

25 The cap 12 is coupled to the drive wheel 17 by a mechanism (not shown) so that the drive wheel 17 rotates together with the cap 12 as the cap 12 is rotated from Figure 4. When the intermediate position of Figure 4 is reached, the next blister 14a is aligned with the blister piercing element 16 and the cap 12 and the drive 30 wheel 17 are de-coupled so that, when the cap 12 is rotated further in the same direction into its fully open position shown in Figure 5, the drive wheel 17 does not rotate together with the cap 12 and so no further indexing or movement of the strip occurs. The last few degrees of movement or overtravel of the cap 12 from its intermediate position shown in Figure 4 to its fully open position shown

in Figure 5 is when the blister piercing element 16 is moved (as explained in more detail below) so as to pierce the lid 14c of said aligned blister which has already stopped moving.

5 Drive mechanisms for connecting the drive wheel 17 to the cap 12 and which allow one component to rotate together with another component when said other component is rotated in only one direction are known from, for example, the previous application referred to above (WO2005/037353 A1). However, the drive mechanism of the embodiments described herein is different to that known  
10 from the aforementioned document because the cap 12 is only coupled to the drive wheel 17 during part of the rotation of the cap 12 in the same direction, i.e. when the intermediate position of the cap 12 has been reached, continued rotation of the cap in the same direction results in rotation of the cap 12 but not the drive wheel 17. The drive mechanism that provides this function is the  
15 subject of a related application but will now be described in more detail with reference to Figures 9 to 14. Although Figures 9 to 14 describes the drive mechanism in relation to a device similar to that shown in the prior art inhaler of Figures 1 and 2, it is equally applicable to the embodiments of the present invention, except that the cap 12 is rotated to index the strip, as opposed to an  
20 actuator 5.

Referring now to Figure 9, there is shown a partial perspective view of an inhalation device 50 comprising an indexing mechanism 51 according to an embodiment of the present invention. It will be appreciated that parts of the  
25 housing 52 and internal components such as the blister locating chassis 53 and actuator 54 are only partially shown for the purposes of clarity and ease of understanding.

The indexing mechanism 51 includes an indexing wheel 55 comprising four  
30 vanes 55a,55b,55c,55d, each having an enlarged head portion 56a,56b,56c,56d. As is clear from reference to Figures 1 and 2, once a blister strip (not shown in Figures 9 to 15) has passed over the blister locating chassis 53, it passes around

the indexing wheel 55. A blister locates in the space between two vanes 55a,55b,55c,55d so that, as the indexing wheel 55 rotates in response to rotation of the actuator 54, a vane 55a,55b,55c,55d engages a blister located between the vanes 55a,55b,55c,55d so as to drive the strip around the indexing wheel 55 to 5 sequentially move each blister forward by a sufficient distance to move a fresh blister into alignment with a blister piercing element (not shown in Figures 9 to 14).

The indexing mechanism 51 includes a drive coupling member 57 (most clearly 10 shown in Figure 14a and 14b) for selectively or temporarily coupling the actuator 54 to the indexing wheel 55 so that, when coupled, the indexing wheel 55 rotates in response to rotation of the actuator 54 to index the strip. The drive coupling member 57 comprises a shaft 58 defining an axis of rotation "A" (see Figure 14a and 14b) on which the indexing wheel 55 is rotatably received so that it can 15 rotate freely about the shaft 58 about said axis of rotation "A". The actuator 54 is fixedly attached to the drive coupling member 57 (such as by a splined pin - not shown) - that is inserted through the actuator 54, through an aperture 52a (see Figure 13) in the housing 52 and is received within the opening 58a in the shaft 58) so that the drive coupling member 57 rotates together with the actuator 20 54 at all times. The actuator 54, drive coupling member 57 and indexing wheel 55 are all mounted coaxially for rotation about the same axis "A".

The drive coupling member 57 has a circular flange 59 that extends radially from one end of the shaft 58. A portion 60 of the flange is cut-away (see arcuate 25 opening 61 in Figure 8) over an angle of approximately 180 degrees where the flange 59 joins the shaft 58 so that this portion 60 of the flange 59 is not directly attached to the shaft 58 but only to the remaining portion of the flange 59 at each of its ends 60a,60b. As a result, this portion 60 of the flange 59 is flexible relative to the rest of the flange 59 and can be deflected out of the plane of the 30 flange 59 that extends at right angles to the axis of the shaft, in an axial direction (indicated by "T" and "S", in Figure 14a and Figure 14b) either towards or away from the shaft 58 or, more importantly, towards or away from the indexing

wheel 55 which is mounted on the shaft 58, when force is applied to it. This flexible flange portion 60 hinges about an axis B which intersects the axis A of the shaft 58 and actuator 54 but extends at right angles to it. The drive coupling member 57, or at least the flange 59, is made from a resilient material so that

5 when the deflected flexible flange portion 60 is released, it returns to its neutral, unstressed position, in which it lies coplanar with the remaining fixed portion of the flange 59.

The flexible flange portion 60 has an integrally formed flange deflecting dog 62 projecting radially from its circumferential edge. The flange deflecting dog 62 has first and second angled engaging faces 63,64 on opposite sides. When the drive coupling member 57 is rotated in response to rotation of the actuator 54 in one direction, one of the first or second angled engaging faces 53,54 cooperate with a fixed formation 65 on the housing 52 to cause the flexible flange portion 60 to deflect in a first direction. When the drive coupling member 57 is rotated in the opposite direction, the other angled engaging face cooperates with the formation 65 on the housing 52 to cause the flexible flange portion 60 to deflect in a second, opposite direction, as will be explained in more detail below.

20 The flexible flange portion 60 also has an arcuately shaped indexing wheel drive dog 66 that upstands in an axial direction from its surface towards the indexing wheel 55 in the same direction as the shaft 58 and extends partially around the circumference of the flexible flange portion 60. As will now be explained in more detail below, an end face 66a (see Figure 14a) of the indexing wheel drive dog 66

25 engages a vane 55a,55b,55c,55d of the indexing wheel 55 when the flexible flange portion 60 has been deflected in a first direction, as indicated by arrow "T" in Figure 14b (the flange portion 60 is shown in its deflected position in Figure 14b), so that the indexing wheel 55 is driven together with the drive coupling member 57.

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As mentioned above, the flange deflecting dog 62 engages a formation 65 on the housing 52 when the drive coupling member rotates in response to rotation of

the actuator 54 so as to flex the deflectable portion 60 of the flange 59. This formation 65 comprises first and second arcuately shaped tracks or paths 67, 68 positioned one above the other or spaced from each other in the axial direction. The surface of the innermost track 67 is visible in Figure 9. The lower or 5 outermost track 68 is located beneath it and is visible in Figure 13. The ends of the tracks 67a, 68a have angled faces for reasons that will become apparent.

When the actuator 54 is rotated in a first direction (the direction indicated by arrow "A" in Figure 3), the drive coupling member 57 rotates together with it 10 and the first outwardly facing angled surface 63 on the flange deflecting dog 62 contacts the angled face 67a of the innermost track 67. Further rotation of the drive coupling member 57 causes the flange deflecting dog 62 to ride up onto the surface of the innermost track 67 thereby deflecting the flexible flange portion 60 inwardly, i.e. in a direction into the housing 62 or towards the shaft 58 and 15 the indexing wheel 55 and the direction indicated by arrow "T" in Figure 8b.

When the flexible flange portion 60 has been deflected inwardly in the direction of arrow T, further rotation of the drive coupling member 57 causes the indexing wheel drive dog 66 to engage a vane, which as shown in Figure 9 is vane 55c, of 20 the indexing wheel 55 so that the indexing wheel 55 rotates together with the drive coupling member 57 and drive to the indexing wheel 55 is engaged.

When the end of the innermost track 67 has been reached, the flange deflecting dog 62 falls off the surface of the track 67 and the resilience of the flexible 25 flange portion 60 causes it to return to its original unstressed or neutral position. When the drive coupling member 57 is rotated further, the indexing wheel drive dog 66 no longer engages with the vane 55c of the indexing wheel 55 and instead passes beneath it so the indexing wheel 55 remains stationary. Therefore, drive to the indexing wheel 55 is disengaged, despite continued rotation of the 30 actuator 54 in the same direction.

When the actuator 54 is rotated back in the opposite direction towards its home

position, the second inwardly facing angled surface 64 of the flange deflecting dog 62 now contacts the lower or outermost track 68 so that the flange deflecting dog 62 now rides onto the surface of that second track 68, thereby causing the flexible flange portion 60 to deflect outwardly or in the opposite direction to the direction in which it was previously deflected, i.e in the direction indicated by arrow marked "S" in Figure 8b. Engagement of the flange deflecting dog 62 with the outermost track 68 so as to deflect the flange portion 60 in the opposite direction, enables the drive coupling member 57 to rotate in the opposite direction without any drive to the indexing wheel 55. It will be appreciated that, if the flange portion 60 was not deflected in the opposite direction, the flange deflecting dog 62 would simply engage against the end of the formation 65 in the housing 62 when rotated back in the opposite direction, thereby preventing rotation in the opposite direction or, the flange deflecting dog 62 would travel back over the innermost track 67 deflecting the flexible flange portion 60 in the same direction causing the opposite end 66b of the indexing wheel drive dog 66 to engage with a vane 65b of the indexing wheel 65 thereby driving the indexing wheel 65 backwards rather than leaving it stationary with no drive engaged. Therefore, it is necessary to ensure that the flexible flange portion 60 is deflected in the opposite direction, i.e. in the direction of arrow "S" in Figure 8a, so that there is no drive to the indexing wheel during rotation of the coupling member 67 in the opposite direction.

When the drive deflecting dog 62 reaches the end of the outermost track 68, the flexible flange portion 60 returns to its original unstressed or neutral position, due to its resilience.

In a preferred embodiment, the indexing mechanism 51 also includes means for locking the indexing wheel 55 to prevent its rotation between indexing steps and means for temporarily releasing that lock to allow rotation of the indexing wheel 55 when driven by the indexing wheel drive dog 66. . The lock also improves positional accuracy of the strip and, more specifically, the next blister to be pierced. This locking arrangement will now be described in more detail below.

The blister location chassis 53 comprises a resiliently flexible cantilever arm 70 that extends from the body 53 of the chassis towards the indexing wheel 55. The free end of the cantilever arm 70 has an enlarged head portion 71 comprising a

5 letterbox shaped slot, window or opening 72 in which the head 56c of a vane 55c of the indexing wheel 55 is located. The opening 72 is dimensioned such that the head 56c of the vane 55c (as shown in Figure 9) is a snug fit therein so that rotation of the indexing wheel 55 is prevented. In the normal or home position of the actuator 54, the head 56c of a vane 55c is located in said opening 72 in the

10 cantilever arm 70 of the chassis 53 so that rotation of the indexing wheel 55 is prevented.

When the actuator 54 is rotated and the flange drive dog 62 engages the innermost track 67 so as to deflect the flexible portion of the flange 60 inwardly

15 towards the indexing wheel 55, the indexing wheel drive dog 66 initially engages with a protrusion 71a extending from an inner side of the enlarged head 71 on the cantilever arm 70 of the chassis 53 so that the cantilever arm 70 is deflected outwardly, away from the indexing wheel 55, to free the head 56c of the vane 55c from the slot 72, thereby unlocking the indexing wheel 55. Only once the

20 indexing wheel 55 has been released by the indexing wheel drive dog 66 pushing the cantilever arm 70 away from the indexing wheel 55 does the indexing wheel drive dog 66 subsequently engage a vane 55c of the indexing wheel 55 so that further rotation of the drive coupling member 57 rotates the indexing wheel 55.

25 Prior to the flange drive dog 22 falling off the end of the innermost track 28 and the flexible flange portion 20 returning to its undeflected state due to its resilience, the indexing wheel drive dog 26 no longer pushes against the cantilever arm 30 and so the cantilever arm 30 is free to move back towards the indexing wheel 15. As the cantilever arm 30 is free to move back just prior to

30 rotation of the indexing wheel 15 being completed, the cantilever arm is prevented from moving all the way back by the head 16b of a following vane 15b which contacts the cantilever arm 30. During further rotation of the indexing

wheel, the head 16b slides across the cantilever arm and then drops into the opening 32 thereby allowing the cantilever arm 30 to move all the way back and locking the indexing wheel 15 in position prior to any further rotation of the drive coupling member 17 in response to continued rotation of the actuator 14.

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On the return stroke of the actuator 54, it will be appreciated that deflection of the flexible flange portion 60 in the opposite direction, i.e. in a direction away from the indexing wheel and in the direction indicated by arrow "S" in Figure 8b, also ensures that the indexing wheel drive dog 66 clears the chassis arm 70 10 and so the indexing wheel 55 is not unlocked, thereby preventing any rotation of the indexing wheel 55 during the return stroke.

It will be appreciated that the extent of rotation of the indexing wheel 55 relative to the extent of rotation of the actuator 54 may be controlled by altering the 15 circumferential length of the inner and outer tracks 67,68. If the tracks are made longer, the flexible flange portion 60 will be deflected for a greater proportion of the angle through which the actuator 54 is rotated and so the indexing wheel drive dog 66 will be engaged with the indexing wheel 55 to rotate the indexing wheel 55 throughout that angle. If required, the tracks 67,68 could be made 20 sufficiently long so that the indexing wheel 55 rotates during rotation of the actuator 54 through its entire angle of movement in one direction. Alternatively, the tracks 67,68 could be made shorter to reduce the angle through which the actuator 54 and indexing wheel 55 rotate together. Ideally, the track length can be selected so that the indexing wheel 55 is rotated through a sufficient angle to 25 move the next, unused blister, into alignment with the blister piercing element. Any further rotation of the actuator 54 can either be lost motion, i.e. it performs no function or some other function. For example, if it is the cap which is rotated, the last period of rotation of the cap can operate the actuator to cause it to pierce the lid of said blister that has just been moved into alignment with the 30 blister piercing element.

It will be appreciated that the indexing mechanism 51 is designed to enable a

stroke to be aborted when the actuator 54 or cap has been rotated through an angle which is sufficient to cause initial indexing of the strip but which is not such that the drive to the indexing wheel 55 has disengaged, i.e. a position in which the flange drive dog 62 has not reached the end of the innermost track 67.

5 If the stroke is aborted and the actuator 54 returned to its rest position before drive to the indexing wheel 55 has disengaged, the strip will be driven backwards into its original position as a rear surface 66b of the indexing wheel drive dog 66 will engage a preceding vane 55b to drive the indexing wheel 55 in the opposite direction. It will be appreciated that this has the advantage that the user may  
10 partially open the actuator 54 to enable them to inspect and/or clean a mouthpiece and then close it again without having indexed the strip or pierced a blister.

The flange 59 is provided with a downwardly depending lug 59a (see Figure 8b) that engages with a feature (not shown) on the casework when the actuator or cap has reached its fully open extent, thereby preventing any further rotation of the actuator or cap.

Referring once again to the embodiments of the present invention as shown in  
20 Figures 3 to 8, it is important to emphasise that, in a preferred embodiment, the cap 12 and the drive wheel 17 are de-coupled from each other only when the cap 12 reaches the intermediate position and that the intermediate position is only a few degrees short of the fully open position. Therefore, if a user opens the cap 12 partially and then returns it to its closed position without having passed the  
25 intermediate position, the drive wheel 17 will rotate together with the cap 12 as the cap 12 is rotated back to its closed position, thereby driving the strip backwards (i.e. in the opposite direction to arrow "D" on the drawings) and return the strip 14 to its original position, because the point (i.e. the intermediate position) at which the cap 12 and drive wheel 17 become de-coupled from each  
30 other has not been reached. This has the advantage that the user may open the cap 12 until the intermediate position has almost, but not quite, been reached to enable them to inspect and/or clean the mouthpiece 13 and then close it again

without having indexed the strip 14 or pierced a blister 14b.

Although piercing of an aligned blister 14b occurs after movement of the strip has stopped, it is envisaged that the mechanism could be configured so that de-  
5 coupling of the drive wheel 17 and cap 12 only occurs when the fully open position of the cap 12, as shown in Figure 5, has been reached. In this instance, the blister piercing element 16 will be drawn into and across the lid of a blister as the strip is still being indexed, thereby forming a larger hole than is created when the strip is stationary prior to puncturing by the blister piercing element.

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The inhaler 10 also comprises an actuator 18. The blister piercing element 16 depends from the actuator 18 and the actuator 18 is rotatable in response to rotation of the cap 12 to cause the blister piercing element 16 to pierce the lid 14c of an aligned blister 14b, as will now be described in more detail.

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The inhaler 10 includes a drive element 19 associated with the cap 12 and a link arm 20 rotatably mounted to the housing 11 at point marked "L". The link arm 20 couples the cap 12 to the actuator 18 via the drive element 19 so that, during part of the rotation of the cap 12, the drive element 19 rotates the link arm 20 to 20 cause corresponding rotation of the actuator 18 which draws the blister piercing element 16 into the lid 14c of an aligned blister 14b.

The drive element 19 is rotatable together with the cap 12 and the drive element 19 and cap 12 can be integrally or separately formed, for ease of manufacture, 25 and subsequently attached to each other during assembly. In the illustrated embodiment, the drive element 19 comprises a disc-shaped member having a circumferentially extending recess 21 in its outer surface. The ends of the recess 21 are defined by radially extending walls or shoulders 21a, 21b that cooperate with the link arm 20 to cause it to rotate.

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The link arm 20 comprises a tooth-like protrusion 22 received in the circumferentially extending recess 21 in the disc-shaped member 19. When the

cap 12 is rotated from its closed position shown in Figure 3 to an almost fully open or intermediate position shown in Figure 4, there is no interaction between the tooth 22 and disc-shaped member 19. However, in the position shown in Figure 4, the tooth 22 lies in contact with a first shoulder 21a formed by the 5 recess 21 in the disc-shaped member 19 so that, upon further rotation of the cap 12 from the intermediate position into its fully open position shown in Figure 5, the shoulder 21a pushes against the tooth 22 to rotate the link arm 20 through a short angle necessary to rotate the actuator 18 and draw the blister piercing element 16 into the lid of an aligned blister 14b.

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Although reference is made to the tooth 22 engaging the first shoulder 21a when the cap is almost fully open and, engaging the second shoulder 21b when the cap is almost fully closed, it will be appreciated that the angle or position of the cap 12 between its open and closed positions when the tooth 22 engages with a 15 respective shoulder 21a,21b can be altered by changing the shape of the disc-shaped member, i.e by making the circumferentially extending recess extend over a shorter distance so that the tooth 22 and shoulder 21a,21b engage at a selected position of the cap 12. Alternatively or additionally, the dimensions of the tooth can be altered.

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The link arm 20 is coupled to the actuator 18 so that, as the link arm 20 rotates, the actuator 18 also rotates to draw the blister piercing member 16 downwardly and into the lid 14c of an aligned blister 14b.

25 In the illustrated embodiment, the coupling between the link arm 20 and the actuator 18 comprises a cam drive arrangement. A cam follower 23 in the form of a pin upstands from a surface of the link arm 20 and is slideably received in a cam guide slot 24 formed in the actuator 18. The actuator 18 has a body portion 18a and a leg portion 18b that depends downwardly from the body portion 18a 30 into the housing 11, the cam guide slot 24 being formed in the leg 18b. The link arm 20 and leg 18b overlap slightly so that the pin 23 extending from the link arm 20 is received in the cam guide slot 24 in the leg 18b. It will be appreciated

that the slot 24 is configured such that, as the link arm 20 rotates, the pin 23 travels along the slot 24 which causes the actuator 18 to rotate and cause the blister piercing element 16 to pierce the lid 14c of an aligned blister, as shown in Figure 5.

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The actuator 18 includes a pivot arm 18c extending from the main body 18a and the free end 18d of the pivot arm 18c is pivotally attached to the housing 11. In the illustrated embodiment, the free end 18d of the pivot arm 18c is captured between the mouthpiece 13 and a moulded formation 11a on the housing 11.

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When the cap 12 is rotated in the opposite direction from its open to its closed position, the tooth 22 on the link arm 20 again follows the circumferential recess 21 in the disc-shaped member 19 and there is no cooperation between the disc-shaped member 19 and the link arm 20. However, shortly prior to the cap 12 reaching its fully closed position, the tooth 22 contacts the second shoulder 21b at the opposite end of the recess 21 so that, on further rotation of the cap 12 back to its fully closed position, the shoulder 21b and tooth 22 cooperate so as to rotate the link member 20 back into its original position shown in Figure 3. As the link arm 20 rotates, the pin 23 travels back along the cam slot 24 in the actuator 18 causing the actuator 18 to rotate in the opposite direction and lifting the blister piercing element 16 out of the blister 14b.

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It will be appreciated that in this embodiment the blister piercing element 16 remains in the blister 14b until the cap 12 is almost completely closed, the link arm 20 and drive element 19 only engaging just prior to the cap 12 reaching its fully closed position. However, it will be appreciated that the inhaler can be easily modified so that the blister piercing element 16 is lifted out of the blister 14b much sooner, i.e. prior to the cap 12 reaching its almost fully closed position. As has already been mentioned above, it is also envisaged that rotation of the actuator 18 and so movement of the blister piercing element 16 into the lid of an aligned blister 14b could occur prior to the cap 12 reaching the almost open position shown in Figure 4, and even when the strip is still being indexed

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forward in the direction of arrow "E". In this case, the openings formed in the blister lid 14c will be larger than the blister piercing elements 16 as the strip is still being indexed after the piercing elements have punctured the lid 14c and the blister piercing elements 16 will effectively plough down and across the blister  
5 lid 14c to open a hole which is larger than the blister piercing element 16, thereby enhancing airflow through the blister.

In the embodiment illustrated in Figures 3 to 5, the actuator 18 and mouthpiece 13 are separate components, the mouthpiece 13 being attached or otherwise  
10 immovably fixed to the housing 11. The mouthpiece 13 has a flow path 25 therein for the passage of air and medicament from a punctured blister 14 into the patient's airway and the body portion 18a of the actuator 18 is movably received within the flow path 25 so that the actuator 18 can rotate from the position shown in Figure 4 into the position shown in Figure 5 and back again  
15 during rotation of the cap 12. The body portion 18a of the actuator 18 has passages therein (not shown) for the flow of medicament through the actuator 18 into the flow path in the mouthpiece 13. The blister piercing elements 16 depend from the body portion 18a of the actuator 18 in the vicinity of the passages. The blister piercing elements 16 may also bridge the openings to those  
20 passages so that the punctures in the blister lid 14c are formed directly beneath those openings.

Although, in the present embodiment, the actuator 18 and the mouthpiece 13 are separate components, it is also envisaged that the actuator may be integrated  
25 with the mouthpiece 13 to form a combined mouthpiece/actuator unit which is pivotally mounted to the housing 11. The second embodiment, described below, also takes this configuration.

The second embodiment will now be described with reference to Figures 6a to 8 of the accompanying drawings. The indexing mechanism for driving the blister strip 14 is substantially the same as that described with reference to the first embodiment so no further mention of it will be made here. However, the way in

which the actuator operates is different and so this will now be described in detail.

In the embodiment of Figures 6a to 8, the drive element comprises a profiled 5 cam guide 30 on the cap 12. As with the previous embodiment, the cam guide 30 can be integrally formed or moulded with the cap 12 or, it can be a separate component which is attached to the cap 12 during manufacture or assembly.

In this embodiment, the actuator and mouthpiece are combined to form a 10 mouthpiece/actuator unit 32 having an upper mouthpiece portion 32a which is shaped so that a user can place it between their lips for inhalation. The combined mouthpiece/actuator unit 32 is mounted to the housing for rotation about axis marked "F" in Figures 6a to 8. The mouthpiece/actuator unit 32 includes an integral arm 33 that extends downwardly from the underside of the 15 mouthpiece/actuator unit into the housing 11 and has a cam follower 34, such as a pin, protruding from its free end (i.e. in a direction perpendicular to the plane of the drawing). The cam follower 34 lies in contact with the cam guide 30 on the cap 12.

20 A tensioning spring 35 is located within the combined mouthpiece/actuator unit 32 and extends between the mouthpiece 32 and the housing 11. Although a tension coil spring is illustrated in the drawings, the spring may also be a leaf, loop or torsion spring. As explained in more detail below, the spring 35 is preferably in tension when the cap 12 is in its closed position.

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The cam guide 30 has a profiled surface such that, when the cap 12 is rotated from its closed position shown in Figure 6a and 6b to its open position shown in Figures 7 and 8, the cam follower 34 follows the profiled surface of the cam guide 30, the cam follower 34 being held against the cam guide 30 due to the 30 tensioning force provided by the spring 35. More specifically, the cam guide 30 has a curved upper surface 36 so that the cam follower 34 travels along the curved surface 36 when the cap 12 is opened (in the direction of arrow "J" in

Figure 6b). In a preferred embodiment, the curved surface 36 is formed as an arcuate surface having its axis coaxial with the axis of the cap such that the follower 34 travels along it during opening of the cap but there is no pivotal movement of the mouthpiece/actuator unit 32 during this time and so no further 5 tensioning of the spring 35. However, in another embodiment, the curved surface 36 may be formed such that there is at least some pivotal movement of the mouthpiece/actuator unit 32 during opening of the cap 12, in the direction of arrow "G" in Figure 7, which causes the spring 35 to be tensioned further i.e. the actuator 32 rotates against a biasing force provided by the spring 35. More 10 specifically, the inhaler may be configured such that the mouthpiece/actuator unit 32 moves into its fully raised position during opening of the cap 12, having already been raised to an intermediate position, so as to partially tension the spring, when the cap 12 was closed on a previous stroke (as described below).

15 When the cap 12 reaches its fully open position, as shown in Figures 7 and 8, the cam follower 34 clears the end of the curved surface 36 and is free to drop down into a channel 37 (in the direction of arrow "K" in Figure 6b) formed between two portions of the cam guide 30 to rotate the mouthpiece/actuator 32 and cause the blister piercing element 16 to pierce the lid 14c of an aligned blister 20 14b, as shown in Figure 8. It will be appreciated that the cam follower 34 drops down into the channel 37 under the biasing force stored in the spring 35 when the cam follower 34 clears the end of the curved surface 36. It will be appreciated that when the position shown in Figure 7 is reached, the cam follower 34 will instantaneously drop down the channel 37, as the biasing force 25 of the spring 35 is released, and not remain in the position shown. It is only shown at the top of the channel 37 for ease of understanding.

As the blister piercing element 16 moves so as to pierce the lid 14c of an aligned blister 14b under release of the spring tensioning force provided by the spring 30 35, a reliable and consistent pierce is achieved and it is not possible to partially pierce a blister 14a. As the piercing element 16 is driven by the release of the tensioning force stored in the spring 35, the piercing velocity/force remains the

same each time as it is driven by the spring 35 and is independent of user operation, such as the speed at which the user opens the cap 12.

When the mouthpiece/actuator unit 32 has rotated into its open position shown 5 in Figure 8, the user can now inhale through the mouthpiece/actuator unit 32 to inhale a dose from the blister 14b into their airway. Once inhalation is complete, the user closes the cap 12. When the cap 12 is rotated back towards its closed position, the cam follower 34 follows a return path 37a in the channel 37 (in the direction of arrow "K" in Figure 6b) which preferably lifts the 10 actuator/mouthpiece unit 32 back up into its "home" or initial position shown in Figure 1. During this rotation of the cap 12, tension is generated in the spring 35, keeping the cam follower 34 in contact with the cam guide 30 and loading the spring ready for piercing during the next use. As indicated above, the mouthpiece/actuator unit 32 may be lifted back into its fully raised position 15 during the return stroke of the cap 12 into its closed position so as to fully tension the spring 35. However, it is also envisaged that the mouthpiece/actuator unit 32 may only be partially lifted back towards its raised position and be held in an intermediate position when the cap 12 is fully closed, in which case further lifting of the mouthpiece/actuator unit 32 and tensioning 20 of the spring 35 occurs during the next opening stroke of the cap 12. This arrangement has the further advantage that that the space within the cap 12 does not have to be large enough to contain the mouthpiece/actuator unit 32 in its fully raised position which is necessary when the mouthpiece/actuator unit 32 is raised completely during closure of the cap 12. On the contrary, the space within 25 the cap 12 only has to be sufficient to contain the mouthpiece/actuator unit 32 in its intermediate position as the raised position is only reached when the cap 12 is opened on a subsequent stroke.

In yet another embodiment, there may be no movement of the 30 mouthpiece/actuator unit 32 when the cap 12 is rotated from its open to its closed position. Therefore, there is little or no tension in the spring 35 when the cap 12 is in its closed position. In this case, the mouthpiece/actuator unit 32 is

entirely rotated from its initial position to its raised position during opening of the cap 12 to tension the spring 35. This arrangement has the advantage that the spring 35 is not in a loaded state when the inhaler is not in use, thereby enabling a plastic spring to be used. This embodiment also has the advantage that the 5 space within the cap 12 only has to be sufficient to contain the mouthpiece/actuator unit 32 in its initial position and not in an intermediate or raised position.

Although it is envisaged that de-coupling of the cap 12 and drive wheel 17 will 10 take place when the cap 12 reaches its open position, as shown in Figures 7 and 8, it will be appreciated that decoupling of the cap 12 and drive wheel 17 may also occur prior to the fully open position being reached, as with the first embodiment described above, so that there is some movement or overtravel of the cap 12 towards the open position during which there is no rotation of the 15 drive wheel 17. However, in the most preferred embodiment, de-coupling of the cap and the drive wheel occurs when the cap 12 has been fully opened and no overtravel movement of the cap is required.

The housing 11 and mouthpiece/actuator 32 may cooperate when the raised 20 position of the mouthpiece 32 has been reached to prevent any over rotation of the mouthpiece 32. In particular, an edge 38 of the mouthpiece 32 may engage against a shoulder 39 on the housing 11.

The channel 37 may have a reduced depth portion (not shown) at its end close to 25 where the cam follower 34 emerges from the channel 37 when the cap 12 reaches its closed position and the arm 33 may have a degree of flexibility or resilience such that, when the cap 12 approaches its closed position, the cam follower 34 engages the reduced depth portion of the channel 37 so as to flex the arm 33 (in a direction into the page as shown in the drawings), as the cam follower 34 rides 30 up over the reduced depth portion. When the cam follower 34 clears the channel 37, the resilience in the arm 33 causes it to return to its original state. This ensures that the cam follower 34 cannot pass back down the channel 37 when

the cap 12 is opened in a subsequent stroke, as it is prevented from doing so as the cam follower 34 is blocked by the reduced depth portion of the channel 37. Preferably, there is a gradual reduction in depth extending along at least a part of the channel 37 so that the cam follower 34 travels up onto the reduced depth 5 portion and gradually flexes the arm 33, thereby ensuring that the cam follower 34 always travels in the same direction along the cam slot.

In this second embodiment, the blister piercing element 16 may include an insert 16a that is clipped or otherwise immovably fixed within a flow path channel of 10 the mouthpiece/actuator unit 32. The insert 16a may be removable from the flow path channel for cleaning and/or replacement.

Although the second embodiment has a combined actuator/mouthpiece unit 32, it is also envisaged that the mouthpiece 32 could be fixed to the housing 11, as in 15 the first embodiment described with reference to Figures 3 to 5. In this case, the actuator would be a separate component, similar to the actuator 18 of Figures 3 to 5, that is pivotally mounted with respect to the housing and to the mouthpiece and includes biasing means such that the actuator moves from its initial position into its raised position against a biasing force provided by the biasing means that 20 biases the actuator towards its initial position.

A modified version of the embodiment described with reference to Figures 3 to 5 will now be described, with reference to Figures 15a to 15c. In this embodiment, the mechanism for controlling piercing of an aligned blister is 25 different. The device has an actuator/mouthpiece assembly 75 which is pivotally attached to the housing 11 at one end (for rotation about axis "T" in Figures 15a to 15c). A piercing element 76 is mounted to and depends from the actuator mouthpiece assembly 75.

30 In the embodiment of Figure 15, the link arm that connects the disc-shaped drive element 19 and the mouthpiece/actuator assembly 75 comprises a lever 77 pivotally mounted to the housing at "Q", in the same way that the link arm 20 of

the embodiment of Figures 3 to 5 is pivotally mounted at "L". The lever 77 includes a tooth 78, similar to the tooth 22 in the embodiment of Figures 3 to 5a, for engagement by the drive element 19 so as to rotate the lever 77 about its axis "Q" when the tooth 78 is engaged by the first or second shoulder 21a, 21b of the 5 drive wheel 19 (although the second shoulder 21b is not clearly shown in Figure 15, it is shown in Figure 3b).

A compliant linkage 79 is coupled to and extends between the lever 77 and the mouthpiece/actuator assembly 75 at a position remote from the pivot axis "Q" 10 of the lever 77. The compliant linkage 79 may be a thin strip of flexible resilient material such as metal or plastic and its end 79a remote from the lever 77 is coupled to the mouthpiece/actuator assembly 75 remote from the axis "T".

As can be seen from Figures 15a and 15b, the mouthpiece/actuator assembly 75 15 normally assumes a raised position so that the piercing elements 76 are held out of a blister piercing position. When the intermediate position of the cap 12, as shown in Figure 15b, is reached, further movement of the cap 12 causes the drive wheel 19 to rotate the lever 77 as the first shoulder 21a pushes against the tooth 78 on the lever 77, as with the embodiment of Figures 3 to 5. The lever 77 20 rotates in the downward direction (the direction of arrow "P" as shown in Figure 15c). As the lever 77 rotates, it pulls on the compliant linkage 79, to pull the mouthpiece/actuator assembly 75 in a downward direction so that it rotates about its axis "T" and so the piercing element 76 mounted thereon pierces the lid of an aligned blister to prime the device ready for inhalation.

25 When the cap 12 is rotated back in its opposite direction, the second shoulder 21b on the drive wheel 19 now engages the tooth 78 on the lever 77 thereby causing the lever 77 to rotate back into its original position. The compliant linkage 79 is sufficiently rigid or resilient for it to lift the mouthpiece/actuator 30 assembly 75 back into its original, raised position as shown in Figure 15a.

The compliant linkage 79 has advantages over the link arm and cam arrangement of the embodiment of Figures 3 to 5 because the compliance of the linkage 79 absorbs any mis-alignment or slack between components that may be caused by wear or manufacturing tolerances. It therefore ensures that the piercing elements 5 76 consistently end up in the same position following repeated actuations of the device and prevents them from being pulled down too far into a blister or, not far enough. It will also be appreciated that, due to its compliance, the compliant linkage 79 allows for overtravel of the cap 12. More specifically, it enables the cap 12 to be rotated beyond a position in which the mouthpiece/actuator 10 assembly 75 has rotated downwardly to its fullest extent to pierce a blister, because any overtravel is accommodated in the flexibility of the compliant linkage 79 which simply extends or elongates when the cap 12 is rotated beyond the piercing position, thereby ensuring that the blister is fully pierced and avoiding any overpiercing where the piercing element is forced further into the blister 15 being pierced.

A modified version of the embodiment described with reference to Figures 6 to 8 will now be described, with reference to Figures 16a to 16e. In this embodiment, the coil spring 35 mounted in the mouthpiece/actuator assembly 20 has been replaced with a torsion spring mounted within the housing, together with a gear assembly.

As with the embodiment of Figures 6 to 8, the inhalation device of Figures 16a to 16e has a profiled cam guide 80 on the cap 81 along which a cam follower 82 25 depending from the mouthpiece/actuator assembly 83 is located. As with the embodiment of Figures 6 to 8, the cam follower 82 follows the cam guide 80 as the cap 81 is opened and closed.

In addition to the cam guide 80, the cap 81 is also provided with a toothed gear 30 84 for rotation together with the cap 81. The axis of the toothed gear 84 is coaxial with the axis of rotation of the cap 81. The toothed gear 84, and cam guide 80 may both be formed integrally with the cap 81 for ease of manufacture.

The toothed gear 84 is in engagement with a driven toothed gear portion 85 pivotally mounted to the housing for rotation about an axis (indicated by "V" in Figures 10a to 10e). The driven toothed gear portion 85 has a pin 86 upstanding 5 from its surface that cooperates with one end of an arm 87 of a torsion spring 88 mounted coaxially with the axis of rotation "F" of the mouthpiece/actuator assembly 83.

10 The arm 87 of the torsion spring 88 is biased against the pin 86 upstanding from the surface of the driven gear portion 85 and has a second arm 89 that extends within and is coupled to the mouthpiece/actuator assembly 83.

15 When the cap 61 is closed, as shown in Figure 16a, there is substantially no loading of the torsion spring 88, or very little loading, to prevent movement of the components. However, when the cap 81 is rotated, the driven toothed gear portion 85 rotates (in the direction of arrow "M" as shown in Figure 16b), as it is coupled to the toothed gear 84. As it rotates, the arm 87 is deflected so as to load the torsion spring 88 thereby biasing the mouthpiece/actuator assembly 83 in a downward direction about axis "F".

20

The mouthpiece/actuator assembly 83 is initially prevented from rotating about its axis "F" by the cam follower 82 which follows the profiled surface of the cam guide 80, until the position shown in Figure 16c is reached. As with the embodiment of Figures 6 to 8, the cam follower 82 initially travels along a 25 curved upper surface 90 of the cam guide 80, in the direction of arrow "J". The cam follower 82 follows the outside profile of the cam guide 80 as a blocking element (not shown) prevents the cam follower 82 from following the cam guide 80 in the opposite direction, i.e. into the channel 92a, when the position shown in Figure 16b has been reached.

30

When the cap 81 has reached its fully open position, as shown in Figure 16c, the tension in the torsion spring 88 has reached its maximum and the cam follower

82 clears the end of the curved upper surface 90 so that it is now free to drop down into the first portion of the channel 92 (in the direction of arrow "K" in Figure 10c) under the load now stored in the torsion spring 88, thereby allowing the mouthpiece/actuator assembly 83 to rotate about its axis "F" and cause a  
5 blister piercing element mounted to the mouthpiece/actuator assembly 83 to pierce the lid of an aligned blister, as shown in Figure 16d. The device is now primed and ready for inhalation.

Once inhalation is complete, the user rotates the cap 81 in the opposite  
10 direction, as shown in Figure 16e. As with the embodiment of Figures 6 to 8, the cam follower 82 follows a return path 92a, as shown in Figure 10e, which lifts the mouthpiece/actuator assembly 83 back into the raised or home position of Figure 16a.

15 It will be appreciated that, in this embodiment, there is very little tension maintained in the spring 88 when the mouthpiece/actuator assembly 83 is in its home or raised position and prior to any opening of the cap 81.

It will be appreciated that there are a number of significant differences between  
20 the embodiments of Figures 3 to 5 and 15 and the embodiments of Figures 6 to 8 and 16. In particular, in the embodiments of Figures 3 to 5 and 15, continued rotation of the cap through a relatively small angle of approximately 10 degrees causes piercing, whereas in the embodiment of Figures 6 to 8 and 16, the spring mechanism operates on a "trigger" basis and does not require continued rotation  
25 of the cap. Furthermore, the embodiments of Figures 3 to 5 and 15 load a spring (the compliant linkage) only as a result of overtravel of the cap, whereas the embodiments of Figures 6 to 8 and 16 allow for charging of a spring over a wide angle of rotation of the cap.

30 It will be appreciated that a "trigger" type of mechanism provides the advantage that piercing occurs nearly instantaneously after indexing and there is no overtravel of the cap required once a dose has reached a piercing position.

Furthermore, the trigger type mechanism is geared lower and requires lower peak torque from a user.

A final embodiment of inhalation device will now be described with reference to  
5 Figures 17a to 17f. This embodiment is similar to the embodiment described with reference to Figures 6 to 8 or Figure 15 in that it has a mouthpiece/actuator assembly 100 which is pivotally mounted to the housing 11 at one end for rotation about an axis "F". A cam follower 101 depends from the other end of the mouthpiece/actuator assembly 100 and is located in a continuous racetrack 10 10 or cam guide 102 defined around the periphery of an island 103 formed as part of the cap 104. As with the embodiments of Figures 6 to 8 and Figure 16, a spring (not shown in Figure 17) is tensioned as the cap 104 is initially opened and the cam follower 101 travels around the cam guide 102. At the same time, a blister is indexed towards a blister piercing position.

15

However, part of the island 103 has a resiliently deformable region 103a. In its unstressed state, the region 103a extends into the cam guide 102 so as to block the path of the cam follower 101. However, due to the flexibility of region 103a, continued rotation of the cap 104 causes the cam follower 101 to deflect the 20 flexible region 103a out of its way. Once the cam follower 101 has passed the flexible region 103a, it springs back up into its original unstressed state and thereby prevents the cam follower 101 from moving backwards along the cam guide 102. The flexible region 103a therefore acts as a latch. Once the cam follower 101 has cleared the latch, the cap 104 cannot be returned to its home 25 position until the cap 104 has been opened to its fullest extent and a blister has been pierced. The latch is positioned such that a strip has been fully indexed to move a blister into a piercing position once the cam follower 101 has past the flexible region 103a.

30 In Figure 17a, the cap 104 is closed and a spring (not shown) for tensioning the mouthpiece actuator assembly 100 is in an unstressed or very lightly stressed state. As with the embodiment of Figures 6 to 8 and 16, when the cap 104 is

opened, the cam follower 101 follows an upper surface of the cam guide 102, as shown in Figure 17b. When the position shown in Figure 17c is reached, the cam follower 101 contacts the flexible region 103a of the island 103. Up to this point, the cap 104 can be returned to its home position and blister will be moved

5 backwards. However, once the cam follower 101 has deflected the region 103a out of the way and has allowed the flexible region 103a to spring back into its original position behind the cam follower 101, as shown in Figure 17d, movement of the cam follower 101 back along the cam guide 102 is prevented by the flexible region 103a. At this point a blister has been fully indexed into a

10 blister piercing position and any further movement of the cap 104 causes the cam follower 101 to drop off the end of the island 103, into the position shown in Figure 17e, causing the spring force to pierce the aligned blister. When the cap 104 is rotated back towards its closed position, as shown in Figure 17f, the cam follower 101 follows the lower part of the cam guide 102 until the position

15 shown in Figure 17a is reached once again.

Many modifications and variations of the invention falling within the terms of the following claims will be apparent to those skilled in the art and the foregoing description should be regarded as a description of the preferred embodiments of

20 the invention only. For example, although reference is made to a "mouthpiece", the invention is also applicable to devices in which the dose is inhaled through the nasal passages. Therefore, for the purposes of this specification, the term "mouthpiece" should also be construed so as to include within its scope a tube which is inserted into the nasal passages of a patient for inhalation therethrough.

25

It will be appreciated that the inhalation device of the present invention may be used in conjunction with a spiral wound element and/or a fixed or flexible wall separating a chamber containing unused blisters from a chamber that receives the used blisters. Such modifications are known from the Applicant's own earlier

30 European patent applications nos. 07111998.6 and 07111996.0.

It will be appreciated that the inhaler of the invention may be either a passive or active

device. In a passive device, the dose is entrained in a flow of air caused when the user inhales through the mouthpiece. However, in an active device, the inhaler would include means for generating a pressurised flow of gas or air through the blister to entrain the dose and carry it out of the blister through the mouthpiece and into the 5 user's airway. In one embodiment, the inhaler may be provided with a source of pressurised gas or air within the housing.

A variety of medicaments may be administered alone by using an inhaler of the invention. Specific active agents or drugs that may be used include, but are not limited 10 to, agents of one or more of the following classes listed below.

- 1) Adrenergic agonists such as, for example, amphetamine, apraclonidine, bitolterol, clonidine, colterol, dobutamine, dopamine, ephedrine, epinephrine, ethynorepinephrine, fenoterol, formoterol, guanabenz, guanfacine, 15 hydroxyamphetamine, isoetharine, isoproterenol, isotharine, mephenterine, metaraminol, methamphetamine, methoxamine, methpentermine, methyldopa, methylphenidate, metaproterenol, metaraminol, mitodrine, naphazoline, norepinephrine, oxymetazoline, pemoline, phenylephrine, phenylethylamine, phenylpropanolamine, pirbuterol, prenalterol, procaterol, propylhexedrine, pseudo- 20 ephedrine, ritodrine, salbutamol, salmeterol, terbutaline, tetrahydrozoline, tramazoline, tyramine and xylometazoline.
- 2) Adrenergic antagonists such as, for example, acebutolol, alfuzosin, atenolol, betaxolol, bisoprolol, bopindolol, bucindolol, bunazosin, butyrophophenes, carteolol, carvedilol, celiprolol, chlorpromazine, doxazosin, ergot alkaloids, esmolol, haloperidol, 25 indoramin, ketanserin, labetalol, levobunolol, medroxalol, metipranolol, metoprolol, nebivolol, nadolol, naftopidil, oxprenolol, penbutolol, phenothiazines, phenoxybenzamine, phentolamine, pindolol, prazosin, propafenone, propranolol, sotalol, tamsulosin, terazosin, timolol, tolazoline, trimazosin, urapidil and yohimbine.
- 3) Adrenergic neurone blockers such as, for example, bethanidine, debrisoquine, 30 guabenzan, guanadrel, guanazodine, guanethidine, guanoclor and guanoxan.
- 4) Drugs for treatment of addiction, such as, for example, buprenorphine.

- 5) Drugs for treatment of alcoholism, such as, for example, disulfiram, naloxone and naltrexone.
- 6) Drugs for Alzheimer's disease management, including acetylcholinesterase inhibitors such as, for example, donepezil, galantamine, rivastigmine and tacrin.
- 5 7) Anaesthetics such as, for example amethocaine, benzocaine, bupivacaine, hydrocortisone, ketamine, lignocaine, methylprednisolone, prilocaine, proxymetacaine, ropivacaine and tyrothricin.
- 8) Angiotensin converting enzyme inhibitors such as, for example, captopril, cilazapril, enalapril, fosinopril, imidapril hydrochloride, lisinopril, moexipril
- 10 hydrochloride, perindopril, quinapril, ramipril and trandolapril.
- 9) Angiotensin II receptor blockers, such as, for example, candesartan, cilexetil, eprosartan, irbesartan, losartan, medoxomil, olmesartan, telmisartan and valsartan.
- 10) Antiarrhythmics such as, for example, adenosine, amidodarone, disopyramide, flecainide acetate, lidocaine hydrochloride, mexiletine, procainamide, propafenone and
- 15 quinidine.
- 11) Antibiotic and antibacterial agents (including the beta-lactams, fluoroquinolones, ketolides, macrolides, sulphonamides and tetracyclines) such as, for example, aclarubicin, amoxicillin, amphotericin, azithromycin, aztreonam chlorhexidine, clarithromycin, clindamycin, colistimethate, dactinomycin, dirithromycin, doripenem,
- 20 erythromycin, fusafungine, gentamycin, metronidazole, mupirocin, natamycin, neomycin, nystatin, oleandomycin, pentamidine, pimaricin, probenecid, roxithromycin, sulphadiazine and triclosan.
- 12) Anti-clotting agents such as, for example, abciximab, acenocoumarol, alteplase, aspirin, bemiparin, bivalirudin, certoparin, clopidogrel, dalteparin, danaparoid,
- 25 dipyridamole, enoxaparin, epoprostenol, eptifibatide, fondaparinux, heparin (including low molecular weight heparin), heparin calcium, lepirudin, phenindione, reteplase, streptokinase, tenecteplase, tinzaparin, tirofiban and warfarin.
- 13) Anticonvulsants such as, for example, GABA analogs including tiagabine and vigabatrin; barbiturates including pentobarbital; benzodiazepines including alprazolam,
- 30 chlordiazepoxide, clobazam, clonazepam, diazepam, flurazepam, lorazepam, midazolam, oxazepam and zolazepam; hydantoins including phenytoin; phenyltriazines including lamotrigine; and miscellaneous anticonvulsants including acetazolamide,

carbamazepine, ethosuximide, fosphenytoin, gabapentin, levetiracetam, oxcarbazepine, piracetam, pregabalin, primidone, sodium valproate, topiramate, valproic acid and zonisamide.

14) Antidepressants such as, for example, tricyclic and tetracyclic antidepressants  
5 including amineptine, amitriptyline (tricyclic and tetracyclic amitriptyline), amoxapine, butriptyline, cianopramine, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dosulepin, dothiepin, doxepin, imipramine, iprindole, levoprotiline, lofepramine, maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortriptyline, opipramol, propizepine, protriptyline, quinupramine, setiptiline, tianeptine  
10 and trimipramine; selective serotonin and noradrenaline reuptake inhibitors (SNRIs) including clovoxamine, duloxetine, milnacipran and venlafaxine; selective serotonin reuptake inhibitors (SSRIs) including citalopram, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, milnacipran, nomifensine, oxaprotiline, paroxetine, sertraline, sibutramine, venlafaxine, viqualine and zimeldine; selective noradrenaline reuptake  
15 inhibitors (NARIs) including demexiptiline, desipramine, oxaprotiline and reboxetine; noradrenaline and selective serotonin reuptake inhibitors (NASSAs) including mirtazapine; monoamine oxidase inhibitors (MAOIs) including amiflamine, brofaromine, clorgyline,  $\alpha$ -ethyltryptamine, etoperidone, iproclozide, iproniazid, isocarboxazid, mebanazine, medifoxamine, moclobemide, nialamide, pargyline,  
20 phenelzine, pheniprazine, pirlindole, procarbazine, rasagiline, safrazine, selegiline, toloxatone and tranylcypromine; muscarinic antagonists including benactyzine and dibenzepin; azaspirones including buspirone, gepirone, ipsapirone, tandospirone and tiaspirone; and other antidepressants including acetaphenazine, ademetionine, S-adenosylmethionine, adrafinil, amesergide, amineptine, amperozide, benactyzine,  
25 benmoxine, binedaline, bupropion, carbamazepine, caroxazone, cericlamine, cotinine, fezolamine, flupentixol, idazoxan, kitanserin, levoprotiline, lithium salts, maprotiline, medifoxamine, methylphenidate, metralindole, minaprine, nefazodone, nisoxetine, nomifensine, oxflozane, oxitriptan, phenyhydrazine, rolipram, roxindole, sibutramine, teniloxazine, tianeptine, tofenacin, trazadone, tryptophan, viloxazine and zolospirone.  
30 15) Anticholinergic agents such as, for example, atropine, benzatropine, biperiden, cyclopentolate, glycopyrrolate, hyoscine, ipratropium bromide, orphenadine hydrochloride, oxitropium bromide, oxybutinin, pirenzepine, procyclidine,

propantheline, propiverine, telenzepine, tiotropium, trihexyphenidyl, tropicamide and trospium.

16) Antidiabetic agents such as, for example, pioglitazone, rosiglitazone and troglitazone.

5 17) Antidotes such as, for example, deferoxamine, edrophonium chloride, fiumazenil, nalmefene, naloxone, and naltrexone.

18) Anti-emetics such as, for example, alizapride, azasetron, benzquinamide, bestahistine, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, dimenhydrinate, diphenhydramine, diphenidol, domperidone, dolasetron, dronabinol, 10 droperidol, granisetron, hyoscine, lorazepam, metoclopramide, metopimazine, nabilone, ondansetron, palonosetron, perphenazine, prochlorperazine, promethazine, scopolamine, triethylperazine, trifluoperazine, triflupromazine, trimethobenzamide and tropisetron.

19) Antihistamines such as, for example, acrivastine, astemizole, azatadine, 15 azelastine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cinnarizine, clemastine, cyclizine, cyproheptadine, desloratadine, dexmedetomidine, diphenhydramine, doxylamine, fexofenadine, hydroxyzine, ketotifen, levocabastine, loratadine, mizolastine, promethazine, pyrilamine, terfenadine and tripeprazine.

20) Anti-infective agents such as, for example, antivirals (including nucleoside and

20 non-nucleoside reverse transcriptase inhibitors and protease inhibitors) including aciclovir, adefovir, amantadine, cidofovir, efavirenz, famiciclovir, foscarnet, ganciclovir, idoxuridine, indinavir, inosine pranobex, lamivudine, nelfinavir, nevirapine, oseltamivir, palivizumab, penciclovir, pleconaril, ribavirin, rimantadine, ritonavir, ruprintrivir, saquinavir, stavudine, valaciclovir, zalcitabine, zanamivir, zidovudine and interferons;

25 AIDS adjunct agents including dapsone; aminoglycosides including tobramycin;

antifungals including amphotericin, caspofungin, clotrimazole, econazole nitrate, fluconazole, itraconazole, ketoconazole, miconazole, nystatin, terbinafine and

voriconazole; anti-malarial agents including quinine; antituberculosis agents including capreomycin, ciprofloxacin, ethambutol, meropenem, piperacillin, rifampicin and

30 vancomycin; beta-lactams including cefazolin, cefmetazole, cefoperazone, cefoxitin, cephacetrile, cephalexin, cephaloglycin and cephaloridine; cephalosporins, including

cephalosporin C and cephalothin; cephamycins such as cephalexin A, cephalexin B,

cephamycin C, cephapirin and cephadrine; leprostatics such as clofazimine; penicillins including amoxicillin, ampicillin, amylpenicillin, azidocillin, benzylpenicillin, carbenicillin, carfecillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, diphenicillin, heptylpenicillin, hetacillin, metampicillin, methicillin, nafcillin, 2-pentenylpenicillin, penicillin N, penicillin O, penicillin S and penicillin V; quinolones including ciprofloxacin, clinafloxacin, difloxacin, grepafloxacin, norfloxacin, ofloxacin and temafloxacin; tetracyclines including doxycycline and oxytetracycline; miscellaneous anti-infectives including linezolid, trimethoprim and sulfamethoxazole.

21) Anti-neoplastic agents such as, for example, droloxifene, tamoxifen and toremifene.

22) Antiparkisonian drugs such as, for example, amantadine, andropinirole, apomorphine, baclofen, benserazide, biperiden, benztropine, bromocriptine, budipine, cabergoline, carbidopa, eliprodil, entacapone, eptastigmine, ergoline, galanthamine, lazabemide, levodopa, lisuride, mazindol, memantine, mofegiline, orphenadrine, trihexyphenidyl, pergolide, piribedil, pramipexole, procyclidine, propentofylline, rasagiline, remacemide, ropinerole, selegiline, spheramine, terguride and tolcapone.

23) Antipsychotics such as, for example, acetophenazine, alizapride, amisulpride, amoxapine, amperozide, aripiprazole, benperidol, benzquinamide, bromperidol, buramate, butaclamol, butaperazine, carphenazine, carpipramine, chlorpromazine, chlorprothixene, clozapramine, clomacran, clopenthixol, clospirazine, clothiapine, clozapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, loxapine, melperone, mesoridazine, metofenazate, molindrone, olanzapine, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine, prochlorperazine, promazine, quetiapine, remoxipride, risperidone, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluperidol, triflupromazine, trifluoperazine, ziprasidone, zotepine and zuclopentixol; phenothiazines including aliphatic compounds, piperidines and piperazines; thioxanthenes, butyrophенones and substituted benzamides.

24) Antirheumatic agents such as, for example, diclofenac, heparinoid, hydroxychloroquine and methotrexate, leflunomide and teriflunomide.

25) Anxiolytics such as, for example, adinazolam, alpidem, alprazolam, alseroxlon, amphenidone, azacyclonol, bromazepam, bromisovalum, buspirone, captodiamine,

capuride, carbcloral, carbromal, chloral betaine, chlordiazepoxide, clobenzepam, enciprazine, flesinoxan, flurazepam, hydroxyzine, ipsapiraone, lesopitron, loprazolam, lorazepam, loxapine, mecloqualone, medetomidine, methaqualone, methprylon, metomidate, midazolam, oxazepam, propanolol, tandospirone, trazadone, zolpidem and 5 zopiclone.

26) Appetite stimulants such as, for example, dronabinol.

27) Appetite suppressants such as, for example, fenfluramine, phentermine and sibutramine; and anti-obesity treatments such as, for example, pancreatic lipase inhibitors, serotonin and norepinephrine re-uptake inhibitors, and anti-anorectic agents.

10 28) Benzodiazepines such as, for example, alprazolam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam.

15 29) Bisphosphonates such as, for example, alendronate sodium, sodium clodronate, etidronate disodium, ibandronic acid, pamidronate disodium, isedronate sodium, tiludronic acid and zoledronic acid.

30) Blood modifiers such as, for example, cilostazol and dipyridamol, and blood factors.

20 31) Cardiovascular agents such as, for example, acebutalol, adenosine, amiloride, amiodarone, atenolol, benazepril, bisoprolol, bumetanide, candesartan, captopril, clonidine, diltiazem, disopyramide, dofetilide, doxazosin, enalapril, esmolol, ethacrynic acid, flecanide, furosemide, gemfibrozil, ibutilide, irbesartan, labetolol, losartan, lovastatin, metolazone, metoprolol, mexiletine, nadolol, nifedipine, pindolol, prazosin,

25 32) procainamide, propafenone, propranolol, quinapril, quinidine, ramipril, sotalol, spironolactone, telmisartan, tocainide, torsemide, triamterene, valsartan and verapamil.

33) Calcium channel blockers such as, for example, amlodipine, bepridil, diltiazem, felodipine, flunarizine, gallopamil, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil.

30 34) Central nervous system stimulants such as, for example, amphetamine, brucine, caffeine, dexfenfluramine, dextroamphetamine, ephedrine, fenfluramine, mazindol, methyphenidate, modafinil, pemoline, phentermine and sibutramine.

- 34) Cholesterol-lowering drugs such as, for example, acipimox, atorvastatin, ciprofibrate, colestipol, colestyramine, bezafibrate, ezetimibe, fenofibrate, fluvastatin, gemfibrozil, ispaghula, nictotinic acid, omega-3 triglycerides, pravastatin, rosuvastatin and simvastatin.
- 5 35) Drugs for cystic fibrosis management such as, for example, *Pseudomonas aeruginosa* infection vaccines (eg Aerugen<sup>TM</sup>), alpha 1-antitrypsin, amikacin, cefadroxil, denufosol, duramycin, glutathione, mannitol, and tobramycin.
- 36) Diagnostic agents such as, for example, adenosine and aminohippuric acid.
- 37) Dietary supplements such as, for example, melatonin and vitamins including 10 vitamin E.
- 38) Diuretics such as, for example, amiloride, bendroflumethiazide, bumetanide, chlortalidone, cyclopenthiazide, furosemide, indapamide, metolazone, spironolactone and torasemide.
- 39) Dopamine agonists such as, for example, amantadine, apomorphine, 15 bromocriptine, cabergoline, lisuride, pergolide, pramipexole and ropinerole.
- 40) Drugs for treating erectile dysfunction, such as, for example, apomorphine, apomorphine diacetate, moxisylyte, phentolamine, phosphodiesterase type 5 inhibitors, such as sildenafil, tadalafil, vardenafil and yohimbine.
- 41) Gastrointestinal agents such as, for example, atropine, hyoscyamine, famotidine, 20 lansoprazole, loperamide, omeprazole and rebeprazole.
- 42) Hormones and analogues such as, for example, cortisone, epinephrine, estradiol, insulin, Ostabolin-C, parathyroid hormone and testosterone.
- 43) Hormonal drugs such as, for example, desmopressin, lanreotide, leuprolide, octreotide, pegvisomant, protirelin, salcotonin, somatropin, tetracosactide, thyroxine 25 and vasopressin.
- 44) Hypoglycaemics such as, for example, sulphonylureas including glibenclamide, gliclazide, glimepiride, glipizide and gliquidone; biguanides including metformin; thiazolidinediones including pioglitazone, rosiglitazone, nateglinide, repaglinide and acarbose.
- 30 45) Immunoglobulins.
- 46) Immunomodulators such as, for example, interferon (e.g. interferon beta-1a and interferon beta-1b) and glatiramer.

- 47) Immunosuppressives such as, for example, azathioprine, cyclosporin, mycophenolic acid, rapamycin, sirolimus and tacrolimus.
- 48) Mast cell stabilizers such as, for example, cromoglycate, iodoxamide, nedocromil, ketotifen, tryptase inhibitors and pemirolast.
- 49) Drugs for treatment of migraine headaches such as, for example, almotriptan, alperopride, amitriptyline, amoxapine, atenolol, clonidine, codeine, coproxamol, cyproheptadine, dextropropoxyphene, dihydroergotamine, diltiazem, doxepin, ergotamine, eletriptan, fluoxetine, frovatriptan, isometheptene, lidocaine, lisinopril, lisuride, loxapine, methysergide, metoclopramide, metoprolol, nadolol, naratriptan, nortriptyline, oxycodone, paroxetine, pizotifen, pizotyline, prochlorperazine propanolol, propoxyphene, protriptyline, rizatriptan, sertraline, sumatriptan, timolol, tolfenamic acid, tramadol, verapamil, zolmitriptan, and non-steroidal anti-inflammatory drugs.
- 50) Drugs for treatment of motion sickness such as, for example, diphenhydramine, promethazine and scopolamine.
- 51) Mucolytic agents such as N-acetylcysteine, ambroxol, amiloride, dextrans, heparin, desulphated heparin, low molecular weight heparin and recombinant human DNase.
- 52) Drugs for multiple sclerosis management such as, for example, bencyclane, methylprednisolone, mitoxantrone and prednisolone.
- 53) Muscle relaxants such as, for example, baclofen, chlorzoxazone, cyclobenzaprine, methocarbamol, orphenadrine, quinine and tizanidine.
- 54) NMDA receptor antagonists such as, for example, mementine.
- 55) Nonsteroidal anti-inflammatory agents such as, for example, aceclofenac, acetaminophen, alminoprofen, amfenac, aminopropylon, amixetrine, aspirin, benoxaprofen, bromfenac, bufexamac, carprofen, celecoxib, choline, cinchophen, cinmetacin, clometacin, clopriac, diclofenac, diclofenac sodium, diflunisal, ethenzamide, etodolac, etoricoxib, fenoprofen, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, loxoprofen, mazipredone, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, parecoxib, phenylbutazone, piroxicam, pirprofen, rofecoxib, salicylate, sulindac, tiaprofenic acid, tolfenamate, tolmetin and valdecoxib.

56) Nucleic-acid medicines such as, for example, oligonucleotides, decoy nucleotides, antisense nucleotides and other gene-based medicine molecules.

57) Opiates and opioids such as, for example, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, carbiphene, cipramadol, clonitazene, codeine, codeine phosphate, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, dihydromorphine, diphenoxylate, dipipanone, fentanyl, hydromorphone, L-alpha acetyl methadol, levorphanol, lofentanil, loperamide, meperidine, meptazinol, methadone, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pentazocine, pethidine, phenazocine, pholcodeine, remifentanil, sufentanil, tramadol, and combinations thereof with an anti-emetic.

10 58) Ophthalmic preparations such as, for example, betaxolol and ketotifen.

59) Osteoporosis preparations such as, for example, alendronate, estradiol, estropipate, raloxifene and risedronate.

15 60) Other analgesics such as, for example, apazone, benzpiperylon, benzydamine, caffeine, cannabinoids, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, pentazocine, propacetamol and propoxyphene.

61) Other anti-inflammatory agents such as, for example, B-cell inhibitors, p38 MAP kinase inhibitors and TNF inhibitors.

20 62) Phosphodiesterase inhibitors such as, for example, non-specific phosphodiesterase inhibitors including theophylline, theobromine, IBMX, pentoxifylline and papaverine; phosphodiesterase type 3 inhibitors including bipyridines such as milrinone, amrinone and olprinone; imidazolones such as piroximone and enoximone; imidazolines such as imazodan and 5-methyl-imazodan; imidazo-25 quinoxalines; and dihydropyridazinones such as indolidan and LY181512 (5-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-1,3-dihydro-indol-2-one); dihydroquinolinone compounds such as cilostamide, cilostazol, and vesnarinone; motapizone; phosphodiesterase type 4 inhibitors such as cilomilast, etazolate, rolipram, oglemilast, roflumilast, ONO 6126, tolafentrine and zardaverine, and including quinazolinediones 30 such as nitraquazone and nitraquazone analogs; xanthine derivatives such as denbufylline and arofylline; tetrahydropyrimidones such as atizoram; and oxime carbamates such as filaminast; and phosphodiesterase type 5 inhibitors including

sildenafil, zaprinast, vardenafil, tadalafil, dipyridamole, and the compounds described in WO 01/19802, particularly (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine, 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-

5 morpholinoethyl)carbamoyl]-pyrimidine, and (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]-pyrimidine).

63) Potassium channel modulators such as, for example, cromakalim, diazoxide, glibenclamide, levcromakalim, minoxidil, nicorandil and pinacidil.

10 64) Prostaglandins such as, for example, alprostadil, dinoprostone, epoprostanol and misoprostol.

15 65) Respiratory agents and agents for the treatment of respiratory diseases including bronchodilators such as, for example, the  $\beta_2$ -agonists bambuterol, bitolterol, broxaterol, carmoterol, clenbuterol, fenoterol, formoterol, indacaterol, levalbuterol, metaproterenol, orciprenaline, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline and the like; inducible nitric oxide synthase (iNOS) inhibitors; the antimuscarinics ipratropium, ipratropium bromide, oxitropium, tiotropium, glycopyrrolate and the like; the xanthines aminophylline, theophylline and the like; adenosine receptor antagonists, cytokines such as, for example, interleukins and interferons; cytokine antagonists and chemokine antagonists including cytokine synthesis inhibitors, endothelin receptor antagonists, elastase inhibitors, integrin inhibitors, leukotriene receptor antagonists, prostacyclin analogues, and ablukast, ephedrine, epinephrine, fenleuton, iloprost, irlukast, isoetharine, isoproterenol, montelukast, ontazolast, pranlukast, pseudoephedrine, sibenadet, tepoxalin, verlukast, 25 zafirlukast and zileuton.

26 66) Sedatives and hypnotics such as, for example, alprazolam, butalbital, chlordiazepoxide, diazepam, estazolam, flunitrazepam, flurazepam, lorazepam, midazolam, temazepam, triazolam, zaleplon, zolpidem, and zopiclone.

30 67) Serotonin agonists such as, for example, 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane, buspirone, m-chlorophenylpiperazine, cisapride, ergot alkaloids, gepirone, 8-hydroxy-(2-N,N-dipropylamino)-tetraline, ipsaperone, lysergic acid

diethylamide, 2-methyl serotonin, mezacopride, sumatriptan, tiaspirone, trazodone and zacopride.

- 68) Serotonin antagonists such as, for example, amitriptyline, azatadine, chlorpromazine, clozapine, cyproheptadine, dextfenfluramine, R(+)- $\alpha$ -(2,3-  
5 dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol, dolasetron, fenclonine, fenfluramine, granisetron, ketanserin, methysergide, metoclopramide, mianserin, ondansetron, risperidone, ritanserin, trimethobenzamide and tropisetron.
- 69) Steroid drugs such as, for example, alcometasone, beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, butixocort, ciclesonide,  
10 clobetasol, deflazacort, diflucortolone, desoxymethasone, dexamethasone, fludrocortisone, flunisolide, fluocinolone, fluometholone, fluticasone, fluticasone propionate, hydrocortisone, methylprednisolone, mometasone, nandrolone decanoate, neomycin sulphate, prednisolone, rimexolone, rofleponide, triamcinolone and triamcinolone acetonide.
- 15 70) Sympathomimetic drugs such as, for example, adrenaline, dexamfetamine, dipirefin, dobutamine, dopamine, dopexamine, isoprenaline, noradrenaline, phenylephrine, pseudoephedrine, tramazoline and xylometazoline.
- 71) Nitrates such as, for example, glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate.
- 20 72) Skin and mucous membrane agents such as, for example, bergapten, isotretinoin and methoxsalen.
- 73) Smoking cessation aids such as, for example, bupropion, nicotine and varenicline.
- 74) Drugs for treatment of Tourette's syndrome such as, for example, pimozide.
- 25 75) Drugs for treatment of urinary tract infections such as, for example, darifenacin, oxybutynin, propantheline bromide and tolteridine.
- 76) Vaccines.
- 77) Drugs for treating vertigo such as, for example, betahistine and meclizine.
- 78) Therapeutic proteins and peptides such as acylated insulin, glucagon, glucagon-  
30 like peptides, exendins, insulin, insulin analogues, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, insulin zinc, isophane insulins, neutral, regular and insoluble insulins, and protamine zinc insulin.

79) Anticancer agents such as, for example, anthracyclines, doxorubicin, idarubicin, epirubicin, methotrexate, taxanes, paclitaxel, docetaxel, cisplatin, vinca alkaloids, vincristine and 5-fluorouracil.

80) Pharmaceutically acceptable salts or derivatives of any of the foregoing.

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It should be noted that drugs listed above under a particular indication or class may also find utility in other indications. A plurality of active agents can be employed in the practice of the present invention. An inhaler according to the invention may also be used to deliver combinations of two or more different active agents or drugs. Specific 10 combinations of two medicaments which may be mentioned include combinations of steroids and  $\beta_2$ -agonists. Examples of such combinations are beclomethasone and formoterol; beclomethasone and salmeterol; fluticasone and formoterol; fluticasone and salmeterol; budesonide and formoterol; budesonide and salmeterol; flunisolide and formoterol; flunisolide and salmeterol; ciclesonide and formoterol; ciclesonide and salmeterol; mometasone and formoterol; and mometasone and salmeterol. Specifically, 15 inhalers according to the invention may also be used to deliver combinations of three different active agents or drugs.

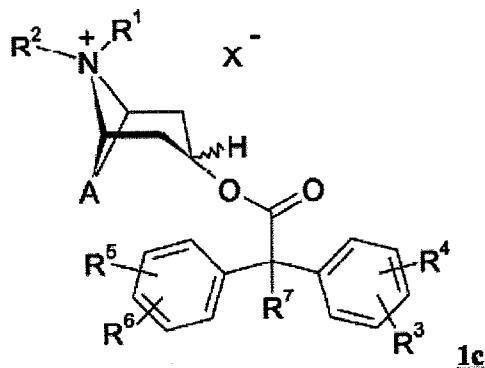
It will be clear to a person of skill in the art that, where appropriate, the active agents or 20 drugs may be linked to a carrier molecule or molecules and/or used in the form of prodrugs, salts, as esters, or as solvates to optimise the activity and/or stability of the active agent or drug.

Anticholinergic agents are referred to above (see No. 15). It is also envisaged that the 25 pharmaceutical composition may comprise one or more, preferably one, anticholinergic 1, optionally in combination with a pharmaceutically acceptable excipient.

The anticholinergic 1 can be selected from the group consisting of

30 a) tiotropium salts 1a,

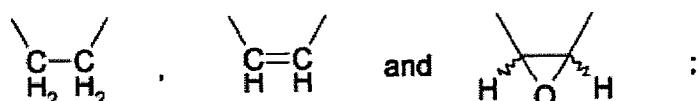
b) compounds of formula 1c



wherein

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A denotes a double-bonded group selected from among



10 **X**<sup>-</sup> denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

15 **R**<sup>1</sup> and **R**<sup>2</sup> which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

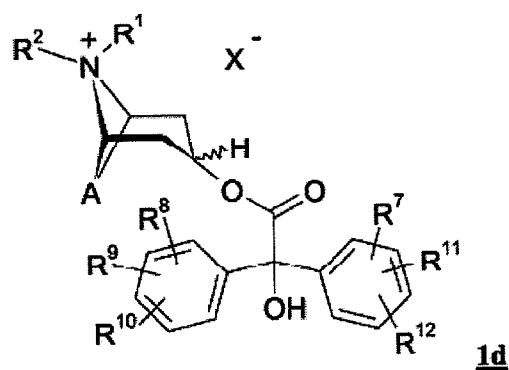
20 **R**<sup>3</sup>, **R**<sup>4</sup>, **R**<sup>5</sup> and **R**<sup>6</sup>, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF<sub>3</sub> or NO<sub>2</sub>;

**R**<sup>7</sup> denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, -CH<sub>2</sub>-F, -CH<sub>2</sub>-CH<sub>2</sub>-F, -O-CH<sub>2</sub>-F, -O-CH<sub>2</sub>-CH<sub>2</sub>-F, -CH<sub>2</sub>-OH, -CH<sub>2</sub>-CH<sub>2</sub>-OH, CF<sub>3</sub>, -CH<sub>2</sub>-OMe, -

CH<sub>2</sub>-CH<sub>2</sub>-OMe, -CH<sub>2</sub>-OEt, -CH<sub>2</sub>-CH<sub>2</sub>-OEt, -O-COMe, -O-COEt, -Q-COCF<sub>3</sub>, -Q-COCF<sub>3</sub>, fluorine, chlorine or bromine;

c) compounds of formula 1d

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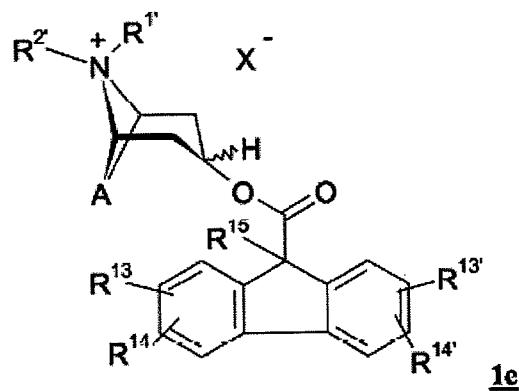
wherein

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A, X<sup>-</sup>, R<sup>1</sup> and R<sup>2</sup> may have the meanings as mentioned hereinbefore and wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF<sub>3</sub> or NO<sub>2</sub>, with the proviso that at least one of the groups R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> is not hydrogen,

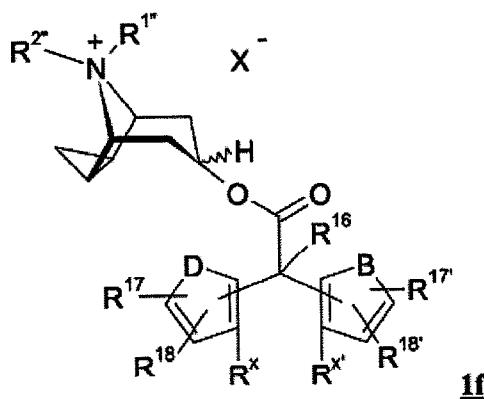
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d) compounds of formula 1e



wherein A and X<sup>+</sup> may have the meanings as mentioned hereinbefore, and wherein R<sup>15</sup> denotes hydrogen, hydroxy, methyl, ethyl, -CF<sub>3</sub>, CHF<sub>2</sub> or fluorine; R<sup>1'</sup> and R<sup>2'</sup> which may be identical or different denote C<sub>1</sub>-C<sub>5</sub>-alkyl which may optionally be substituted by C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, hydroxy or halogen, or R<sup>1'</sup> and R<sup>2'</sup> together denote a -C<sub>3</sub>-C<sub>5</sub>-alkylene-bridge; R<sup>13</sup>, R<sup>14</sup>, R<sup>13'</sup> and R<sup>14'</sup> which may be identical or different denote hydrogen, -C<sub>1</sub>-C<sub>4</sub>-alkyl, -C<sub>1</sub>-C<sub>4</sub>-alkyloxy, hydroxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, CN, NO<sub>2</sub> or halogen,

e) compounds of formula 1f



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wherein  $X^-$  may have the meanings as mentioned hereinbefore, and wherein

15 D and B which may be identical or different, preferably identical, denote -O, -S, -NH, -CH<sub>2</sub>, -CH=CH, or -N(C<sub>1</sub>-C<sub>4</sub>-alkyl)-;

$R^{16}$  denotes hydrogen, hydroxy,  $-C_1-C_4$  alkyl,  $-C_1-C_4$  alkyloxy,  $-C_1-C_4$  alkylene-Halogen,  $-O-C_1-C_4$  alkylene-halogen,  $-C_1-C_4$  alkylene-OH,  $-CF_3$ ,  $CHF_2$ ,  $-C_1-C_4$  alkylene- $C_1-C_4$  alkyloxy,  $-O-COC_1-C_4$  alkyl,  $-O-COC_1-C_4$  alkylene-halogen,  $-C_1-C_4$  alkylene- $C_3-C_6$  cycloalkyl,  $-O-COCF_3$  or halogen;

$R^{1''}$  and  $R^{2''}$  which may be identical or different, denote  $-C_1-C_5$ -alkyl, which may optionally be substituted by  $-C_3-C_6$ -cycloalkyl, hydroxy or halogen, or

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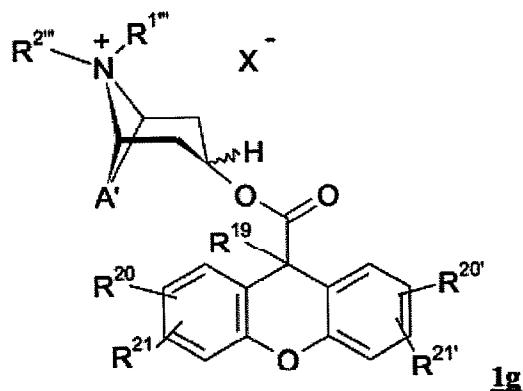
R<sup>1"</sup> and R<sup>2"</sup> together denote a -C3-C5-alkylene bridge;

R<sup>17</sup>, R<sup>18</sup>, R<sup>17'</sup> and R<sup>18'</sup>, which may be identical or different, denote hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, hydroxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, CN, NO<sub>2</sub> or halogen;

5 R<sup>x</sup> and R<sup>x'</sup> which may be identical or different, denote hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, hydroxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, CN, NO<sub>2</sub> or halogen or

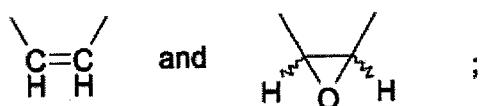
10 R<sup>x</sup> and R<sup>x'</sup> together denote a single bond or a bridging group selected from among the bridges -O-, -S-, -NH-, -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -N(C<sub>1</sub>-C<sub>4</sub>-alkyl), -CH(C<sub>1</sub>-C<sub>4</sub>-alkyl)- and -C(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, and

f) compounds of formula 1g



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wherein X<sup>-</sup> may have the meanings as mentioned hereinbefore, and wherein A' denotes a double-bonded group selected from among



20 R<sup>19</sup> denotes hydroxy, methyl, hydroxymethyl, ethyl, -CF<sub>3</sub>, CHF<sub>2</sub> or fluorine; R<sup>1"</sup> and R<sup>2"</sup> which may be identical or different denote C<sub>1</sub>-C<sub>5</sub>-alkyl which may optionally be substituted by C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, hydroxy or halogen, or

$R^{1''}$  and  $R^{2''}$  together denote a  $-C_3-C_5$ -alkylene-bridge;  
 $R^{20}$ ,  $R^{21}$ ,  $R^{20'}$  and  $R^{21'}$  which may be identical or different denote hydrogen,  $-C_1-C_4$ -alkyl,  $-C_1-C_4$ -alkyloxy, hydroxy,  $-CF_3$ ,  $-CHF_2$ , CN, NO<sub>2</sub> or halogen.

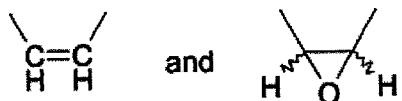
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The compounds of formula 1c are known in the art (WO 02/32899).

In a preferred embodiment of the invention the method comprises administration of compounds of formula 1c, wherein

10  $X^-$  denotes bromide;  
 $R^1$  and  $R^2$  which may be identical or different denote a group selected from methyl and ethyl, preferably methyl;  
 $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$ , which may be identical or different, denote hydrogen, methyl, methyloxy, chlorine or fluorine;  
15  $R^7$  denotes hydrogen, methyl or fluorine, optionally together with a pharmaceutically acceptable excipient.

Of particular importance are compounds of general formula 1c, wherein A denotes a double-bonded group selected from among



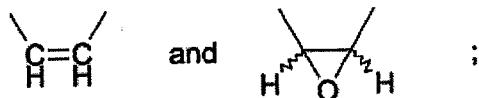
The compounds of formula 1c, may optionally be administered in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

25 Of particular importance within a method according to the invention are the following compounds of formula 1c:  
tropenol 2,2-diphenylpropionic acid ester methobromide,  
scopine 2,2-diphenylpropionic acid ester methobromide,  
scopine 2-fluoro-2,2-diphenylacetic acid ester methobromide and  
30 tropenol 2-fluoro-2,2-diphenylacetic acid ester methobromide.

The compounds of formula 1d are known in the art (WO 02/32898).

In a preferred embodiment of the invention the method comprises administration of  
5 compounds of formula 1d, wherein

A denotes a double-bonded group selected from among



**X**<sup>-</sup> denotes bromide;

10 R<sup>1</sup> and R<sup>2</sup> which may be identical or different denote methyl or ethyl, preferably methyl;

R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup>, which may be identical or different, denote hydrogen, fluorine, chlorine or bromine, preferably fluorine with the proviso that at least one of the groups R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> not hydrogen, optionally together with a  
15 pharmaceutically acceptable excipient.

Of particular importance within the method according to the invention are the following compounds of formula 1d:

20 tropenol 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,  
scopine 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,  
scopine 4,4'-difluorobenzilic acid ester methobromide,  
tropenol 4,4'-difluorobenzilic acid ester methobromide,  
scopine 3,3'-difluorobenzilic acid ester methobromide, and  
tropenol 3,3'-difluorobenzilic acid ester methobromide.

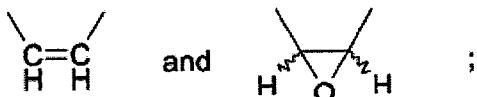
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The pharmaceutical compositions according to the invention may contain the compounds of formula 1d optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

30 The compounds of formula 1e are known in the art (WO 03/064419).

In a preferred embodiment of the invention the method comprises administration of compounds of formula 1e, wherein

A denotes a double-bonded group selected from among



**X<sup>-</sup>** denotes an anion selected from among chloride, bromide and methanesulphonate, preferably bromide;

R<sup>15</sup> denotes hydroxy, methyl or fluorine, preferably methyl or hydroxy;

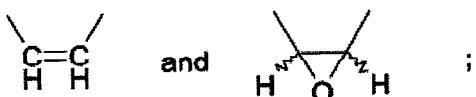
10 R<sup>1'</sup> and R<sup>2'</sup> which may be identical or different represent methyl or ethyl, preferably methyl;

R<sup>13</sup>, R<sup>14</sup>, R<sup>13'</sup> and R<sup>14'</sup> which may be identical or different represent hydrogen, -CF<sub>3</sub>, -CHF<sub>2</sub> or fluorine, preferably hydrogen or fluorine, optionally together with a pharmaceutically acceptable excipient.

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In another preferred embodiment of the invention the method comprises administration of compounds of formula 1e, wherein

A denotes a double-bonded group selected from among



**X<sup>-</sup>** denotes bromide;

R<sup>15</sup> denotes hydroxy or methyl, preferably methyl;

R<sup>1'</sup> and R<sup>2'</sup> which may be identical or different represent methyl or ethyl, preferably methyl;

25 R<sup>13</sup>, R<sup>14</sup>, R<sup>13'</sup> and R<sup>14'</sup> which may be identical or different represent hydrogen or fluorine, optionally together with a pharmaceutically acceptable excipient.

Of particular importance within the method according to the invention are the following compounds of formula 1e:

tropenol 9-hydroxy-fluorene-9-carboxylate methobromide ;  
tropenol 9-fluoro-fluorene-9-carboxylate methobromide;  
5 scopine 9-hydroxy-fluorene-9-carboxylate methobromide;  
scopine 9-fluoro-fluorene-9-carboxylate methobromide;  
tropenol 9-methyl-fluorene-9-carboxylate methobromide;  
scopine 9-methyl-fluorene-9-carboxylate methobromide.

10 The pharmaceutical compositions according to the invention may contain the compounds of formula 1e optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

The compounds of formula 1f are known in the art (WO 03/064418).

15 In another preferred embodiment of the invention the method comprises administration of compounds of formula 1f wherein

$\text{X}^-$  denotes chloride, bromide, or methanesulphonate, preferably bromide;  
20 D and B which may be identical or different, preferably identical, denote -O, -S, -NH or -CH=CH-;  
R<sup>16</sup> denotes hydrogen, hydroxy, -C<sub>1</sub>-C<sub>4</sub>-alkyl, -C<sub>1</sub>-C<sub>4</sub> alkyloxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, fluorine, chlorine or bromine;  
R<sup>17</sup> and R<sup>18</sup> which may be identical or different, denote C<sub>1</sub>-C<sub>4</sub>-alky, which may  
25 optionally be substituted by hydroxy, fluorine, chlorine or bromine, or  
R<sup>17</sup> and R<sup>18</sup> together denote a -C<sub>3</sub>-C<sub>4</sub>-alkylene-bridge;  
R<sup>17</sup>, R<sup>18</sup>, R<sup>17'</sup> and R<sup>18'</sup>, which may be identical or different, denote hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, hydroxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, CN, NO<sub>2</sub>, fluorine, chlorine or bromine;  
R<sup>x</sup> and R<sup>x'</sup> which may be identical or different, denote hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl,  
30 C<sub>1</sub>-C<sub>4</sub>-alkyloxy, hydroxy, -CF<sub>3</sub>, -CHF<sub>2</sub>, CN, NO<sub>2</sub>, fluorine, chlorine or bromine or  
R<sup>x</sup> and R<sup>x'</sup> together denote a single bond or a bridging group selected from among the  
bridges -O, -S, -NH- and -CH<sub>2</sub>- , optionally together with a pharmaceutically

acceptable excipient.

In another preferred embodiment of the invention the method comprises administration of compounds of formula 1f, wherein

5

- X<sup>-</sup>** denotes chloride, bromide, or methanesulphonate, preferably bromide;
- D and B which may be identical or different, preferably identical, denote -S or -CH=CH-;
- R<sup>16</sup> denotes hydrogen, hydroxy or methyl;
- 10 R<sup>17</sup> and R<sup>27</sup> which may be identical or different, denote methyl or ethyl;
- R<sup>17</sup>, R<sup>18</sup>, R<sup>17'</sup> and R<sup>18'</sup>, which may be identical or different, denote hydrogen, -CF<sub>3</sub> or fluorine, preferably hydrogen;
- R<sup>x</sup> and R<sup>x'</sup> which may be identical or different, denote hydrogen, -CF<sub>3</sub> or fluorine, preferably hydrogen or
- 15 R<sup>x</sup> and R<sup>x'</sup> together denote a single bond or the bridging group -O-, optionally together with a pharmaceutically acceptable excipient.

In another preferred embodiment of the invention the method comprises administration of compounds of formula 1f wherein

20

- X<sup>-</sup>** denotes bromide;
- D and B denote -CH=CH-;
- R<sup>16</sup> denotes hydrogen, hydroxy or methyl;
- R<sup>17</sup> and R<sup>27</sup> denote methyl;
- 25 R<sup>17</sup>, R<sup>18</sup>, R<sup>17'</sup> and R<sup>18'</sup>, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;
- R<sup>x</sup> and R<sup>x'</sup> which may be identical or different, denote hydrogen or fluorine, preferably hydrogen or
- R<sup>x</sup> and R<sup>x'</sup> together denote a single bond or the bridging group -O-, optionally together
- 30 with a pharmaceutically acceptable excipient.

Of particular importance within the method according to the invention are the following compounds of formula 1f:

cyclopropyltropine benzilate methobromide;

cyclopropyltropine 2,2-diphenylpropionate methobromide;

5 cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide; cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide; cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide; cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide; cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.

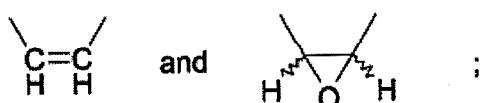
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The pharmaceutical compositions according to the invention may contain the compounds of formula 1f optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

15 The compounds of formula 1g are known in the art (WO 03/064417).

In another preferred embodiment of the invention the method comprises administration of compounds of formula 1g wherein

20 A' denotes a double-bonded group selected from among



X- denotes chloride, bromide or methanesulphonate, preferably bromide;

25 R<sup>19</sup> denotes hydroxy or methyl;

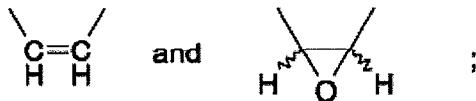
R<sup>1”</sup> and R<sup>2”</sup> which may be identical or different represent methyl or ethyl, preferably methyl;

R<sup>20</sup>, R<sup>21</sup>, R<sup>20’</sup> and R<sup>21’</sup> which may be identical or different represent hydrogen, -CF<sub>3</sub>, -CHF<sub>2</sub> or fluorine, preferably hydrogen or fluorine, optionally together with a

30 pharmaceutically acceptable excipient.

In another preferred embodiment of the invention the method comprises administration of compounds of formula 1g wherein

5 A' denotes a double-bonded group selected from among



X- denotes bromide;

10

R<sup>19</sup> denotes hydroxy or methyl, preferably methyl;

R<sup>1”</sup> and R<sup>2”</sup> which may be identical or different represent methyl or ethyl, preferably methyl;

R<sup>3</sup>, R<sup>4</sup>, R<sup>3’</sup> and R<sup>4’</sup> which may be identical or different represent hydrogen or fluorine,

15 optionally together with a pharmaceutically acceptable excipient.

Of particular importance within the method according to the invention are the following compounds of formula 1g:

tropenol 9-hydroxy-xanthene-9-carboxylate methobromide;

20 scopine 9-hydroxy-xanthene-9-carboxylate methobromide;

tropenol 9-methyl-xanthene-9-carboxylate methobromide;

scopine 9-methyl-xanthene-9-carboxylate methobromide;

tropenol 9-ethyl-xanthene-9-carboxylate methobromide;

tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide;

25 scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide.

The pharmaceutical compositions according to the invention may contain the compounds of formula 1g optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

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The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 5 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless otherwise stated, the definitions propyl and 5 butyl also include all possible isomeric forms of the groups in question. Thus, for example, propyl includes n- propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert. -butyl, etc.

10 The cycloalkyl groups used, unless otherwise stated, are alicyclic groups with 3 to 6 carbon atoms. These are the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. According to the invention cyclopropyl is of particular importance within the scope of the present invention.

15 The alkylene groups used, unless otherwise stated, are branched and unbranched double- bonded alkyl bridges with 1 to 5 carbon atoms. Examples include: methylene, ethylene, propylene or butylene.

20 The alkylene-halogen groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably disubstituted, by a halogen. Accordingly, unless otherwise stated, the term alkylene-OH groups denotes branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by a hydroxy.

25 The alkyloxy groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 5 carbon atoms which are linked via an oxygen atom. The following may be mentioned, for example: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless otherwise stated, the 30 definitions propyloxy and butyloxy also include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec. butyloxy and tert. -butyloxy, etc. The

word alkoxy may also possibly be used within the scope of the present invention instead of the word alkyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to as methoxy, ethoxy, propoxy or butoxy.

5 The alkylene-alkyloxy groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 5 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

10 The -O-CO-alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are bonded via an ester group. The alkyl groups are bonded directly to the carbonylcarbon of the ester group. The term -O-CO-alkyl-halogen group should be understood analogously. The group -O-CO-CF<sub>3</sub> denotes trifluoroacetate.

15 Within the scope of the present invention halogen denotes fluorine, chlorine, bromine or iodine. Unless otherwise stated, fluorine and bromine are the preferred halogens. The group CO denotes a carbonyl group.

20 The inhalation device according to the invention comprises the compounds of formula 1 preferably in admixture with a pharmaceutically acceptable excipient to form a powder mixture. The following pharmaceutically acceptable excipients may be used to prepare these inhalable powder mixtures according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol),  
25 salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose and trehalose are the particularly preferred excipients, while lactose, preferably in form of its monohydrate is most particularly preferred.  
30

The compounds of formula 1 may be used in the form of their racemates, enantiomers

or mixtures thereof. The separation of enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.).

5 Optionally, the inhalation device according to the invention contains plural of doses of a medicament in powder form that contains, beside one compound of formula 1, another active ingredient.

Preferably the additional active ingredient is a beta<sub>2</sub> agonists 2 which is selected from the group consisting of albuterol, bambuterol, bitolterol, broxaterol, carbuterol, 10 clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenot, sulphronterol, tiaramide, terbutaline, tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3- (4-{6-[2-Hydroxy-2-(4-hydroxy-3- hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide, 5-[2-(5,6- Diethyl-indan-2-ylamino)-l-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one , 4-hydroxy-7- [2- { [2- { [3 -(2-phenylethoxy)propyl] sulphonyl} ethyl] -amino } ethyl] -2(3H)-benzothiazolone , 1 -(2-fluoro-4-hydroxyphenyl)-2-[4-(1 -benzimidazolyl)-2-methyl-2-butylamino]ethanol , 1 - [3 -(4-methoxybenzyl-amino)-4-hydroxyphenyl] -2- [4-(1 -benzimidazolyl)-2-methyl-2-butylamino]ethanol , 1 -[2H-5-hydroxy-3-oxo-4H-1 ,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol , 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol , 1 -[2H-5-hydroxy-3 -OXO-4H- 1 ,4-benzoxazin-8-yl] -2- [3 -(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol , 1 - [2H-5-hydroxy-3 -oxo-4H- 1 ,4-benzoxazin-8-yl] -2- {4- [3 -(4- methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol , 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert.-butylamino)ethanol and 1 -(4-ethoxycarbonylamino-3-cyano- 5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

According to the instant invention more preferred beta<sub>2</sub> agonists 2 are selected from the group consisting of bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphoterol, terbutaline, tolubuterol, 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide, 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[4-(3-(4-methoxyphenyl)-1,2,4-triazol-3-yl)-2-methyl-2-butylamino]ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert-butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

More preferably, the betamimetics 2 used as within the compositions according to the invention are selected from among fenoterol, formoterol, salmeterol, 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide, 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[4-(3-(4-methoxyphenyl)-1,2,4-triazol-3-yl)-2-methyl-2-butylamino]ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert-butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

benzoxazin-8-yl] -2- {4- [3 -(4-methoxyphenyl)- 1 ,2,4-triazol-3 -yl] -2-methyl-2-butylamino}ethanol , optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts thereof, and the hydrates thereof. Of the betamimetics mentioned above the

5 compounds formoterol, salmeterol, 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]- hexyloxy}-butyl)-benzenesulfoneamide, and 5-[2-(5,6-Diethyl-indan-2-ylamino)-l- hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one are particularly preferred, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts thereof, and the

10 hydrates thereof. Of the betamimetics mentioned above the compounds formoterol and salmeterol are particularly preferred, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts thereof, and the hydrates thereof.

15 Examples of pharmacologically acceptable acid addition salts of the betamimetics 2 according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, l-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid, 5-(2,4- difluorophenyl)salicylic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts 2.

According to the invention, the salts of the betamimetics 2 selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate, maleate and xinafoate are preferred.

25 Particularly preferred are the salts of 2 in the case of salmeterol selected from among the hydrochloride, sulphate, 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate and xinafoate, of which the 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate and especially xinafoate are particularly important. Particularly preferred are the salts of 2 in the case of formoterol selected from the hydrochloride, sulphate and fumarate, of which the hydrochloride and fumarate are particularly preferred, such as formoterol fumarate.

Salts of salmeterol, formoterol, 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy} -butyl)-benzenesulfoneamide, and 5-[2-(5,6-Diethyl-indan- 2-ylamino)-l-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one , are preferably used as

5 the betamimetics 2 according to the invention. Of particular importance are salmeterol and formoterol salts. Any reference to the term betamimetics 2 also includes a reference to the relevant enantiomers or mixtures thereof. In the pharmaceutical compositions according to the invention, the compounds 2 may be present in the form of their racemates, enantiomers or mixtures thereof. The separation of the enantiomers from

10 the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.) If the compounds 2 are used in the form of their enantiomers, it is particularly preferable to use the enantiomers in the R configuration at the C-OH group.

15 Optionally, the inhalation device according to the invention contains plural of doses of a medicament in powder form that contains beside one compound of formula 1 a steroid 3 as another active ingredient.

In such medicament combinations the steroid 3 is preferably selected from among

20 prednisolone, prednisone , butixocortpropionate, RPR- 106541, flunisolide , beclomethasone , triamcinolone , budesonide , fluticasone , mometasone , ciclesonide , rofleponide , ST- 126 , dexamethasone , (S)-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-17 $\alpha$ -[(2-furanylcarbonyl)oxy] - 11 [beta]-hydroxy- 16 $\alpha$ -methyl-3 -oxo-androsta- 1 ,4-diene- 17 $\beta$ -carbothionate , (S)-(2-oxo-tetrahydro-furan-3S-yl)6 $\alpha$ ,9 $\alpha$ -difluoro-1 1  $\beta$ -hydroxy- 16 $\alpha$ -

25 methyl-3 -oxo- 17 $\alpha$ -propionyloxy-androsta- 1 ,4-diene- 17 $\beta$ -carbothionate, and etiprednol- dichloroacetate (BNP- 166), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

30 In particularly preferred medicament combinations the steroid 3 is selected from the group comprising flunisolide , beclomethasone , triamcinolone , budesonide ,

fluticasone, mometasone, ciclesonide, rofleponide, ST- 126, dexamethasone, (S)-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro- 1 Ia- [(2-furanylcarbonyl)oxy] - 11  $\beta$ -hydroxy- 16 $\alpha$ -methyl-3 -oxo-androsta- 1,4-diene-17 $\beta$ -carbothionate, (S)-(2-oxo-tetrahydro-furan-3S-yl)6 $\alpha$ ,9 $\alpha$ -difluoro-1 1 $\beta$ - hydroxy- 16 $\alpha$ -methyl-3 -oxo- 17 $\alpha$ -propionyloxy-androsta- 1,4-5 diene- 17 $\beta$ -carbothionate, and etiprednol-dichloroacetate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

In particularly preferred medicament combinations the steroid 3 is selected from the 10 group comprising budesonide, fluticasone, mometasone, ciclesonide, (S)-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro- 1 Ia- [(2-furanylcarbonyl)oxy] - 11  $\beta$ -hydroxy- 16 $\alpha$ -methyl-3 -oxo-androsta- 1 ,A- diene-17 $\beta$ -carbothionate, and etiprednol-dichloroacetate, 15 optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

Any reference to steroids 3 includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the 20 steroids 3 may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furcates.

Optionally, the inhalation device according to the invention contains plural of doses of a medicament on powder form that contains beside one compound of formula 1 25 additionally both, one of the betamimetics 2 mentioned hereinbefore and one of the steroids 3 mentioned hereinbefore.

According to one aspect, there is provided an inhalation device according to the invention, wherein each blister contains a pharmaceutical composition in powder form 30 wherein the pharmaceutical composition comprises one or more, preferably one,

compound of formula 1.

Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250 $\mu\text{m}$ , preferably between 10 and 5 150 $\mu\text{m}$ , most preferably between 15 and 80 $\mu\text{m}$ . It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9 $\mu\text{m}$  to the excipients mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance I-, and optionally 2 and/or 3, 10 preferably with an average particle size of 0.5 to 10 $\mu\text{m}$ , more preferably from 1 to 6 $\mu\text{m}$ , is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and finally mixing the ingredients together are known from the prior art.

15 For the methods of preparing the pharmaceutical compositions in powder form reference may be made to the disclosure of WO 02/30390, WO 03/017970, or WO 03/017979 for example. The disclosure of WO 02/30390, WO 03/017970, and WO 03/017979 is hereby incorporated by reference into the instant patent application in its entirety.

20 As an example, the pharmaceutical compositions according to the invention may be obtained by the method described below.

First, the excipient and the active substance are placed in a suitable mixing container.

25 The active substance used has an average particle size of 0.5 to 10  $\mu\text{m}$ , preferably 1 to 6  $\mu\text{m}$ , most preferably 2 to 5  $\mu\text{m}$ . The excipient and the active substance are preferably added using a sieve or a granulating sieve with a mesh size of 0.1 to 2 mm, preferably 0.3 to 1 mm, most preferably 0.3 to 0.6 mm. Preferably, the excipient is put in first and then the active substance is added to the mixing container. During this mixing process 30 the two components are preferably added in batches. It is particularly preferred to sieve in the two components in alternate layers. The mixing of the excipient with the active

substance may take place while the two components are still being added. Preferably, however, mixing is only done once the two components have been sieved in layer by layer.

- 5 If after being chemically prepared the active substance used in the process described above is not already obtainable in a crystalline form with the particle sizes mentioned earlier, it can be ground up into the particle sizes which conform to the above-mentioned parameters (so-called micronising).
- 10 Many modifications and variations of the invention falling within the terms of the following claims will be apparent to those skilled in the art and the foregoing description should be regarded as a description of the preferred embodiments of the invention only.

**Claims**

5     1. An inhaler comprising a housing to receive a strip having a plurality of blisters, each blister having a puncturable lid and containing a dose of medicament for inhalation by a user, a mouthpiece through which a dose of medicament is inhaled by a user, a cap to cover the mouthpiece and, a blister piercing element to pierce the lid of a blister, the cap being rotatable to drive the strip to sequentially move each blister into alignment with the blister piercing element and, an actuator operable in response to rotation of the cap to cause the blister piercing element to puncture the lid of an aligned blister such that, when a user inhales through the mouthpiece, an airflow through the blister is generated to entrain the dose contained therein and carry it out of the blister and via the mouthpiece into the user's airway.

10

15     2. An inhaler according to claim 1, wherein the actuator is pivotally mounted to the housing such that it rotates in response to rotation of the cap to cause the blister piercing element to pierce the lid of an aligned blister.

20

25     3. An inhaler according to claim 2, comprising a link arm that couples the cap to the actuator to rotate the actuator in response to rotation of the cap.

30

25     4. An inhaler according to claim 3, wherein the link arm is pivotally mounted to the housing.

35

25     5. An inhaler according to claim 4, wherein the link arm is coupled to the actuator so that the actuator rotates relative to the housing to draw the blister piercing element into the lid of an aligned blister when the link arm rotates.

40

30     6. An inhaler according to claim 4, comprising a compliant linking member coupling the link arm to the actuator.

7. An inhaler according to claim 6, wherein the compliant linking member is formed from a resilient strip that is configured to deform in response to the application of a force thereto which is greater than the force required to pivot 5 the actuator into a piercing position.
8. An inhaler according to claim 5, including cooperating cam elements on the actuator and on the link arm such that rotation of the link arm causes rotation of the actuator to draw the blister piercing element into the lid of an 10 aligned blister.
9. An inhaler according to claim 8, wherein the cooperating cam elements comprise a cam follower on the link arm and a cam guide on the actuator, the cam follower and cam guide being configured such that the cam follower follows 15 the cam guide when the link arm rotates to rotate the actuator.
10. An inhaler according to claim 9, wherein the cam guide comprises a slot in the actuator and the cam follower comprises a pin on the link arm slideably received in the slot.

20

11. An inhaler according to claim 10, wherein the link arm comprises a plate and the actuator includes a leg extending into the housing, the plate and leg having a region of overlap, the pin upstanding from the plate and being received in the slot in said region of overlap.

25

12. An inhaler according to any of claims 3 to 11, comprising a link arm drive element rotatable together with the cap, the drive element and link arm being configured such that they cooperate with each other for part of the rotation of the cap so that the link arm rotates when the user rotates the cap.

30

13. An inhaler according to claim 12, wherein the drive element and link arm are configured such that they cooperate when the cap has almost reached its

open position so that further rotation of the cap into the open position rotates the link arm.

14. An inhaler according to claim 13, wherein the drive element and link arm  
5 are configured such that they cooperate when the cap has almost reached its closed position so that further rotation of the cap into its closed position rotates the link arm in the opposite direction back to its original position.

15. An inhaler according to any of claims 12 to 14, wherein the link arm drive element comprises a first shoulder that engages the link arm to rotate the link arm when the cap is rotated from its closed to its open position and, a second shoulder that engages the link arm to rotate the link arm in the opposite direction when the cap is rotated from its open to its closed position.

16. An inhaler according to claim 15, wherein the drive element comprises a disc-shaped member.

17. An inhaler according to any of claims 12 to 16, wherein the drive element is integral with the cap.

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18. An inhaler according to claim 16 or 17, wherein the disc has an arcuate recess extending around a portion of its circumference and the first and second shoulders are defined by radially extending walls at each end of the arcuate recess.

25

19. An inhaler according to claim 18, wherein the link arm includes a tooth, the tooth being received within the arcuate recess in the disc such that the first shoulder contacts the tooth as the cap is rotated from its closed to its open position so that further rotation of the cap causes the first shoulder to push against the tooth to rotate the link arm and, such that the second shoulder contacts the tooth as the cap is rotated from its open to its closed position so

that further rotation of the cap causes the second shoulder to push against the tooth to rotate the link arm in the opposite direction.

20. An inhaler according to claim 1 or claim 2, wherein the cap includes a  
5 profiled cam guide and the actuator includes a cam follower that follows the profile of the cam guide during rotation of the cap.
21. An inhaler according to claim 20, wherein the profiled cam guide is configured such that, as the cap is rotated the cam follower follows the profile so  
10 as to move the actuator from an initial position into a raised position.
22. An inhaler according to claim 21, wherein the profiled cam guide is configured such that the cam follower follows the profile so as to move the actuator from said initial position into said raised position during rotation of the  
15 cap from its open to its closed positions.
23. An inhaler according to claim 22, wherein the profiled cam guide is configured such that the cam follower follows the profile so as to move the actuator from said initial position into said raised position during rotation of the  
20 cap from its closed to its open positions.
24. An inhaler according to claim 21, wherein the profiled cam guide is configured such that the cam follower follows the profile so as to move the actuator from said initial position into an intermediate position during rotation  
25 of the cap from its open to its closed positions and, to move the actuator from said intermediate position to said raised position during rotation of the cap from its closed to its open positions.
25. An inhaler according to any of claims 21 to 24, wherein the profiled cam  
30 guide is integral with the cap.

26. An inhaler according to any of claims 21 to 25, including biasing means associated with the actuator such that the actuator moves from its initial position into its raised position against a biasing force provided by the biasing means that biases the actuator towards its initial position.

5

27. An inhaler according to claim 23 to 25, wherein the cam guide has a curved surface and the cam follower follows the curved surface as the cap is rotated from its closed into its open position.

10 28. An inhaler according to claim 20, wherein a portion of the cam guide has a curved surface and the cam follower follows said portion as the cap is rotated from its closed into its open position.

15 29. An inhaler according to claim 28, wherein the actuator is in a raised position when the cap is closed and remains substantially stationary as the cam follower follows said curved surface of the cam guide during opening of the cap.

20 30. An inhaler according to claim 28 or 29, including a torsion spring and a mechanism to tension the torsion spring in response to rotation of the cap from its closed into its open position.

25 31. An inhaler according to claim 30, wherein the mechanism includes a toothed gear mounted for rotation together with the cap and a driven gear pivotally mounted to the housing and lying in meshing engagement with the toothed gear.

32. An inhaler according to claim 31, wherein the torsion spring comprises an arm cooperatively engaged with the driven gear such that, when the driven gear rotates during opening of the cap, the arm is deflected to tension the torsion 30 spring and bias the actuator assembly in a blister piercing direction.

33. An inhaler according to any of claims 27 to 32, wherein the curved surface ends when the cap reaches its open position, the cam follower falling off the end of the curved surface to release the biasing force and rotate the actuator so that the blister piercing element pierces the lid of an aligned blister.

5

34. An inhaler according to claim 33, wherein the cam guide has a return path and the cam follower follows the return path as the cap is rotated back from its open to its closed position.

10 35. An inhaler according to claim 34, wherein the cam guide comprises two cam guide portions and the return path is defined by a channel between the two cam guide portions.

15 36. An inhaler according to any of claims 20 to 35, wherein the cam follower comprises a pin extending from the actuator.

37. An inhaler according to any of claims 20 to 36, wherein the actuator comprises a leg extending into the housing and the cam follower upstands from a free end of the leg.

20

38. An inhaler according to any of claims 30 to 36, wherein the torsion spring is coaxially mounted with the axis of rotation of the actuator.

25 39. An inhaler according to any of claims 27 to 38, wherein the cam guide comprises a latch mechanism to allow the cam follower to pass along the cam guide in one direction past the latch mechanism.

40. An inhaler according to claim 39, wherein the latch mechanism comprises a flexible region on the cam guide that normally blocks the path of the cam follower in an unstressed state.

30

41. An inhaler according to claim 40, wherein rotation of the cap causes the cam follower to deflect the flexible region out of the way to allow the cam follower to pass the latch.

5 42. An inhaler according to claim 41, wherein the flexible region springs back to its original position once it has been passed by the cam follower, to prevent movement of the cam follower in a backward direction across the latch.

10 43. An inhaler according to any preceding claim, wherein the mouthpiece and actuator are integrated so as to form a mouthpiece/actuator unit, the mouthpiece/actuator unit being operable in response to rotation of the cap to cause the blister piercing element to puncture the lid of an aligned blister such that, when a user inhales through the mouthpiece, an airflow through the blister is generated to entrain the dose contained therein and carry it out of the blister 15 and via the mouthpiece into the user's airway.

44. An inhaler according to claim 43, wherein the mouthpiece/actuator unit comprises an actuator portion and a mouthpiece portion attached to each other.

20 45. An inhaler according to claim 44, wherein the actuator portion and the mouthpiece portion are separable from each other.

46. An inhaler according to any of claims 43 to 45, wherein the mouthpiece/actuator unit includes a flow path for the flow of medicament 25 through the mouthpiece/actuator unit into the patient's airway.

47. An inhaler according to claim 46, wherein the blister piercing element comprises an insert, said insert being located within the flow path in the mouthpiece actuator unit, said insert having openings therein for the passage of 30 medicament therethrough.

48. An inhaler according to claim 47, wherein the blister piercing elements depend from said insert mounted in the flow path.

49. An inhaler according to any of claims 1 to 42, wherein the actuator and 5 mouthpiece are separate components, the mouthpiece being attached to the housing and the actuator being mounted for rotation relative to the mouthpiece and to the housing.

50. An inhaler according to claim 49, wherein the actuator includes a pivot 10 arm, a free end of the pivot arm being pivotally mounted to the housing.

51. An inhaler according to claim 50, wherein the free end of the pivot arm is captured between the mouthpiece and the housing to pivotally mount the end of the pivot arm.

15

52. An inhaler according to any of claims 49 to 51, wherein the mouthpiece includes a flow path for the flow of air and medicament from a punctured blister through the mouthpiece into the patient's airway, a portion of the actuator being movably received within with the flow path in the mouthpiece, said portion 20 having passages therethrough for the flow of air and medicament through said portion.

53. An inhaler according to claim 52, wherein the blister piercing elements depend from said portion of the actuator mounted in the flow path of the 25 mouthpiece.

54. An inhaler according to any preceding claim, comprising an indexing mechanism to sequentially move each blister into alignment with the blister piercing element.

30

55. An inhaler according to claim 54, wherein the indexing mechanism comprises a drive member that engages the blister strip to drive the strip to sequentially move each blister into alignment with the blister piercing element.

5 56. An inhaler according to claim 55, wherein the cap and drive member are configured such that the cap and drive member cooperate on rotation of the cap from a closed position, in which the cap covers the mouthpiece, to an open position, in which the mouthpiece is exposed for inhalation through the mouthpiece, so that the drive member drives the strip and moves a blister into  
10 alignment with the blister piercing element.

15 57. An inhaler according to claim 56, wherein the cap and drive member are configured such that the cap is de-coupled from the drive member as the cap reaches its fully open position, so that there is no drive to a strip as the cap is rotated in the opposite direction from its open position back to its closed position.

20 58. An inhaler according to claim 56, wherein the cap and drive member are configured such that the cap is de-coupled from the drive member before the cap reaches its open position so that there is no drive to a strip as the cap is rotated further in the same direction towards its open position.

25 59. An inhaler according to any of claims 55 to 58, wherein the drive member comprises a drive wheel, the cap and the drive wheel both being mounted to the housing for rotation about the same axis.

60. An inhaler according to any preceding claim containing a strip of blisters each having a puncturable lid and containing a dose of medicament for inhalation by a user.

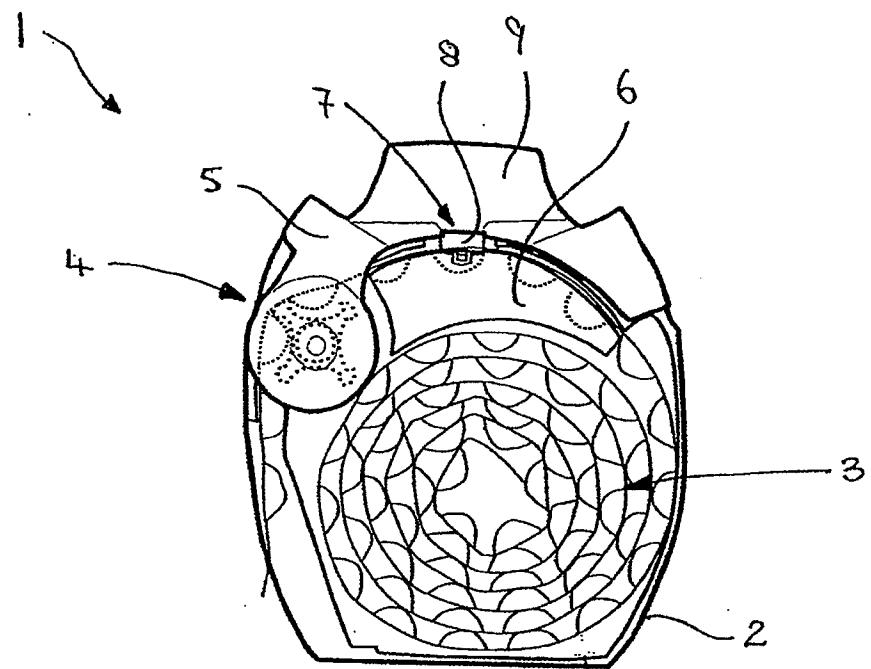


FIGURE 1

(PRIOR ART)

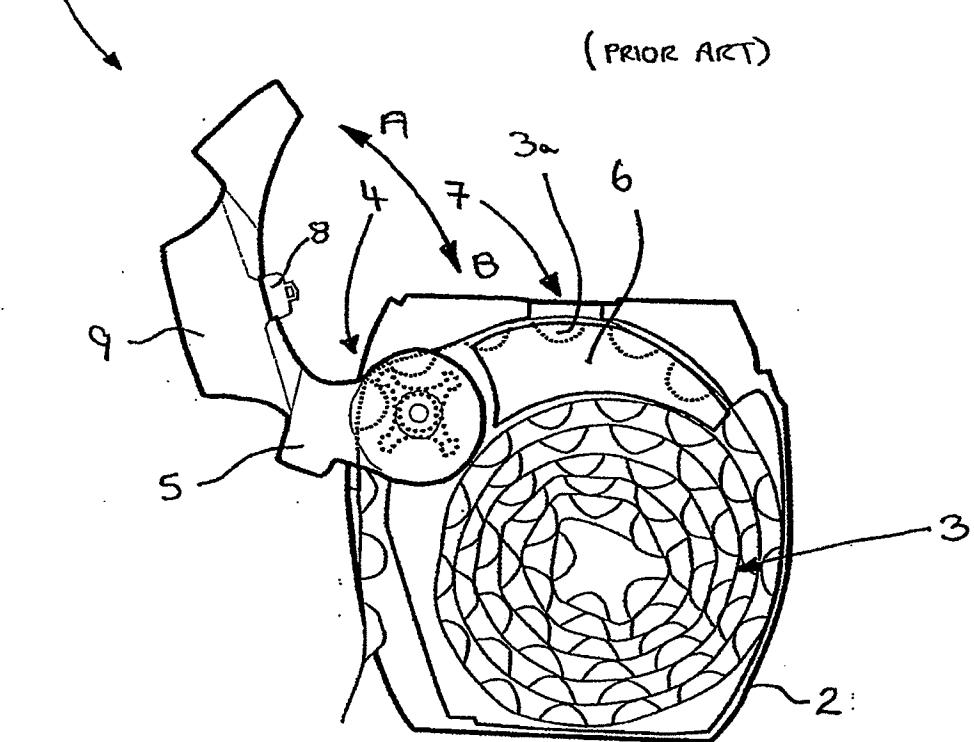


FIGURE 2

(PRIOR ART)

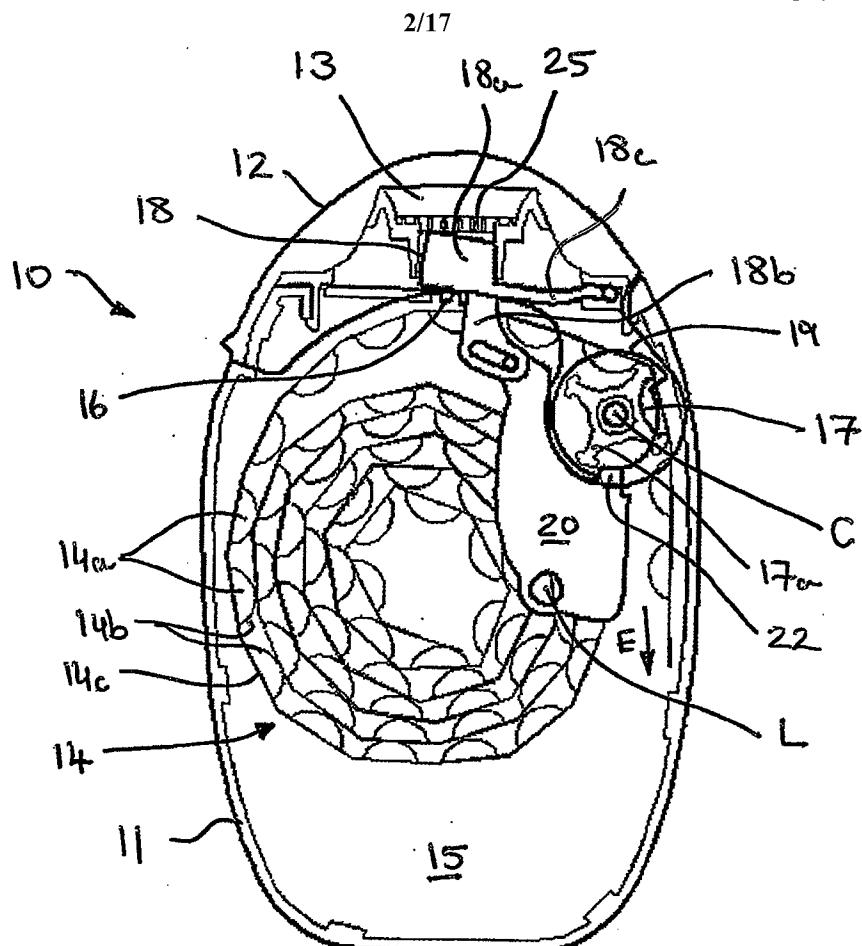


Figure 3a

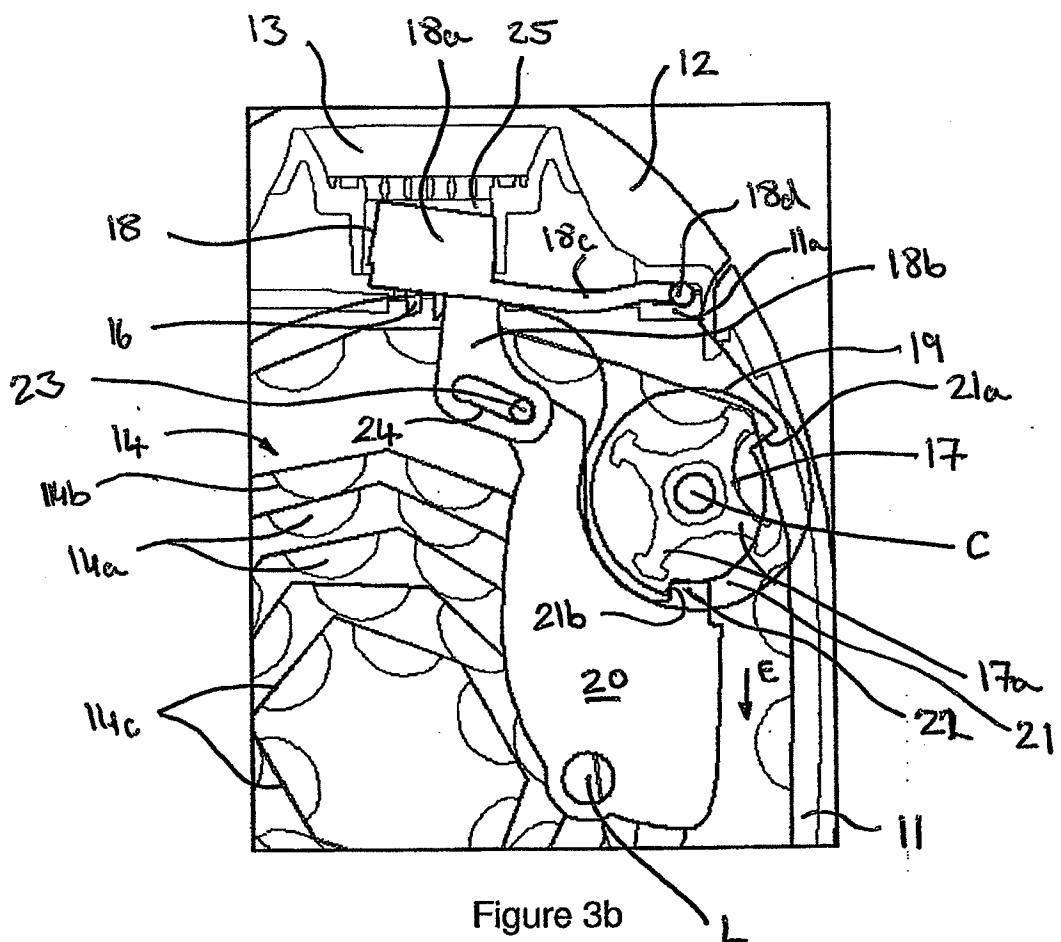


Figure 3b

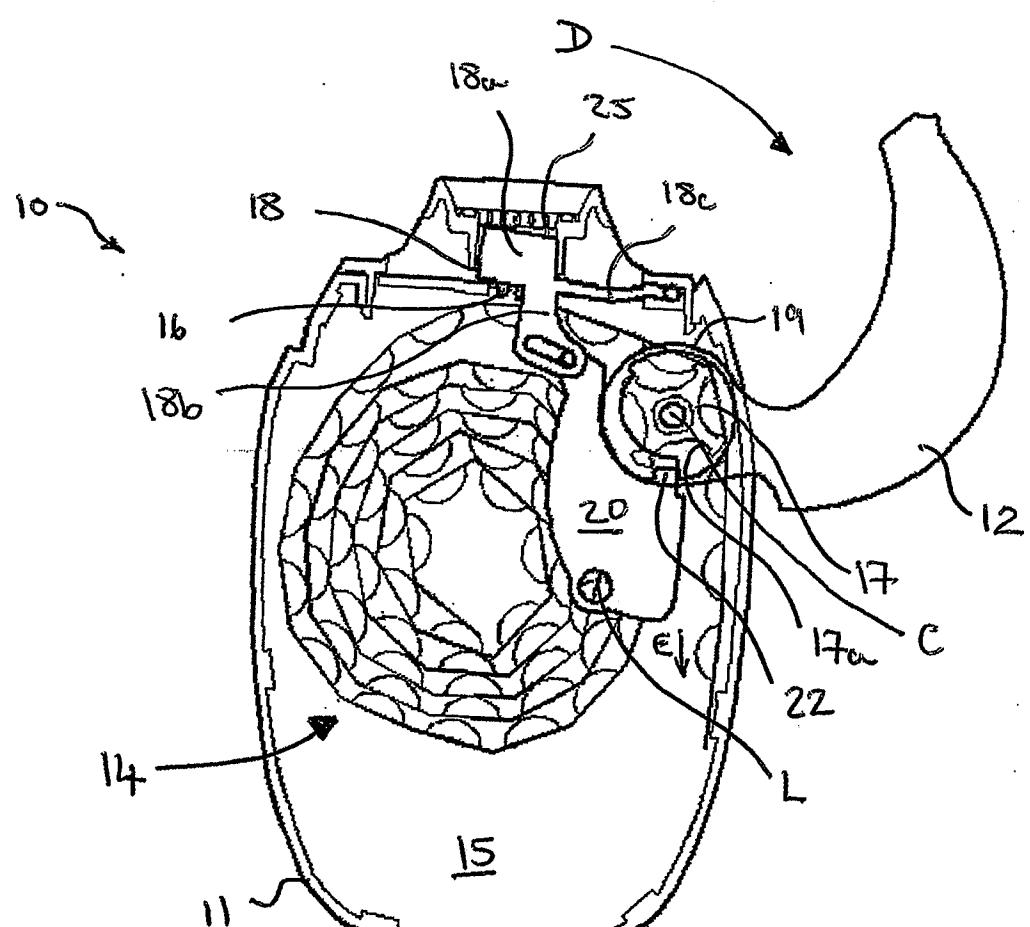


Figure 4

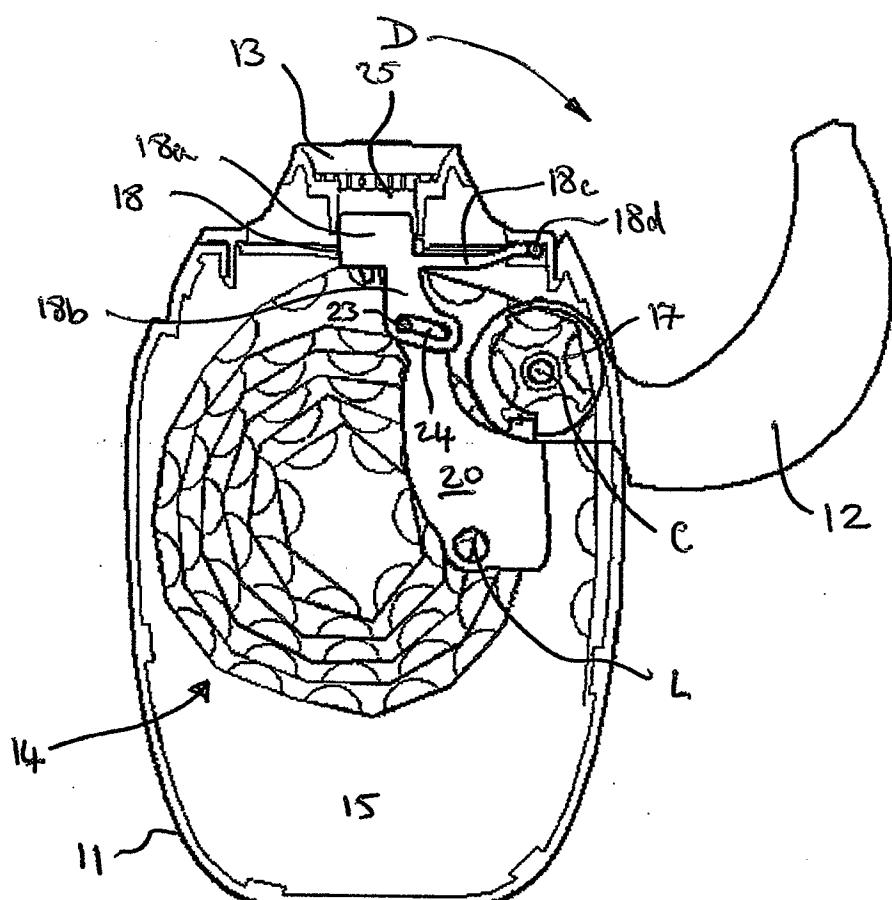


Figure 5

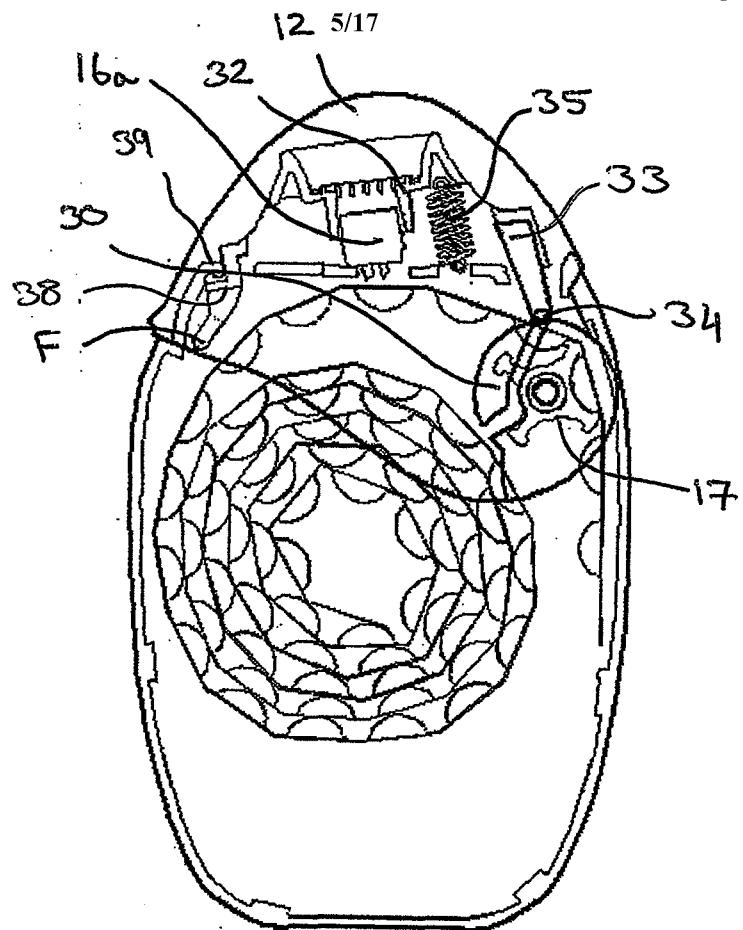


Figure 6a

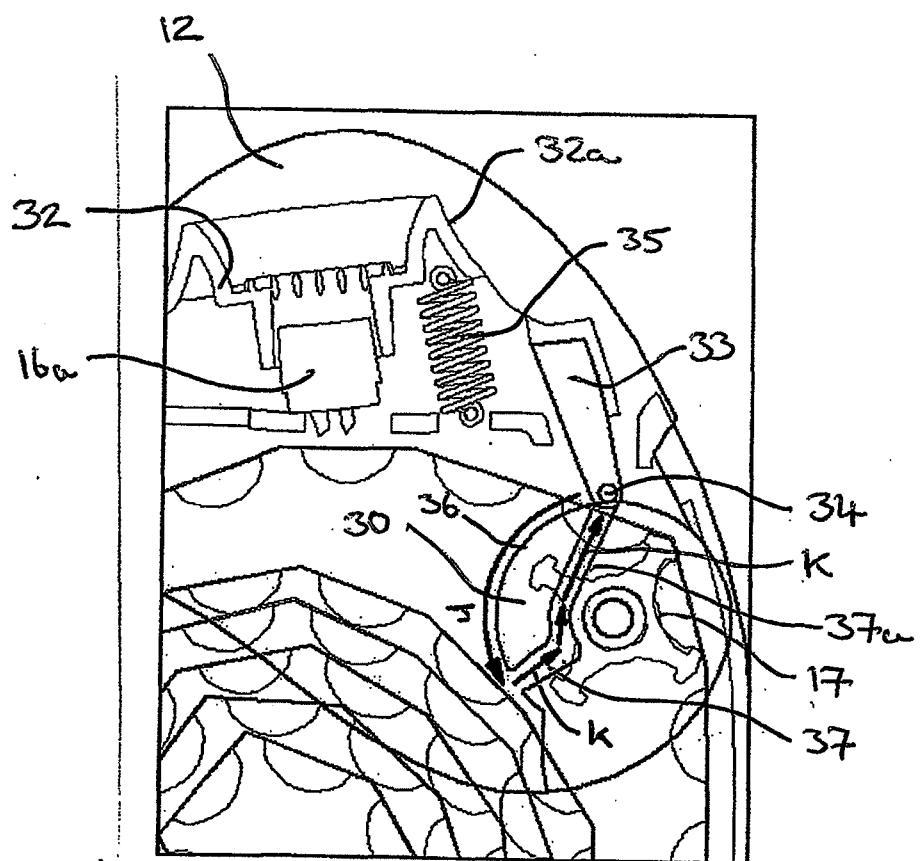


Figure 6b

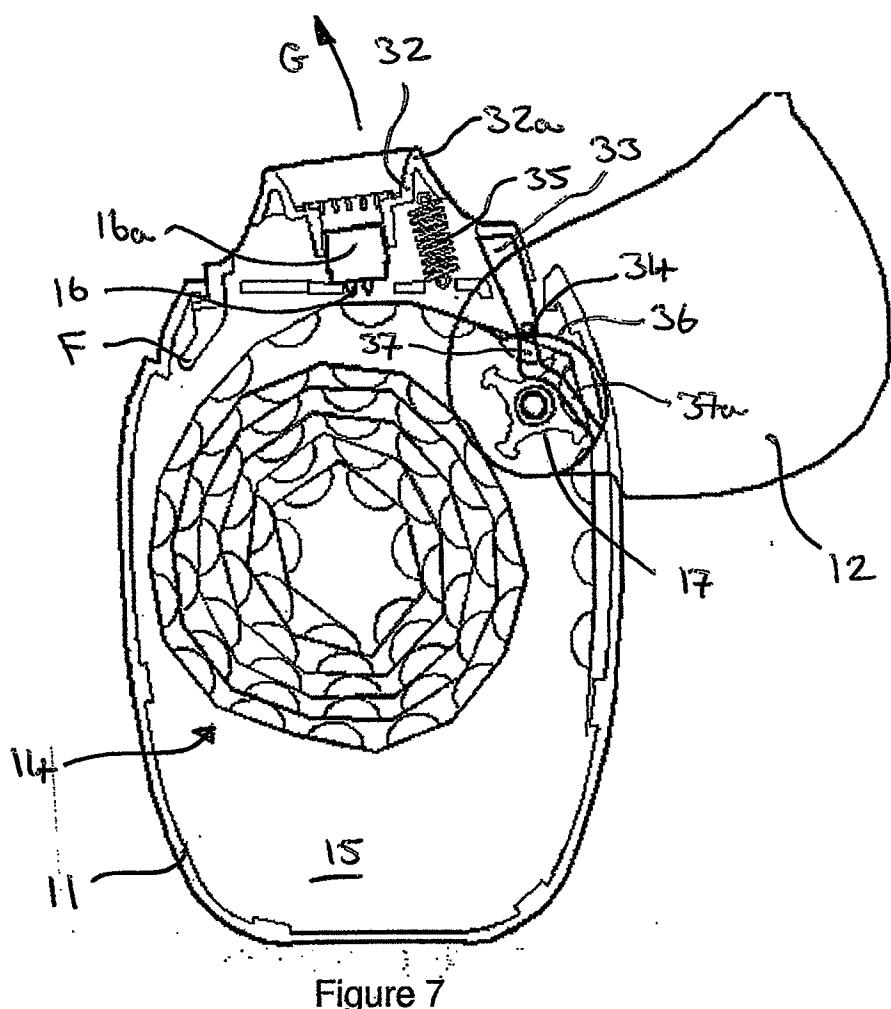


Figure 7

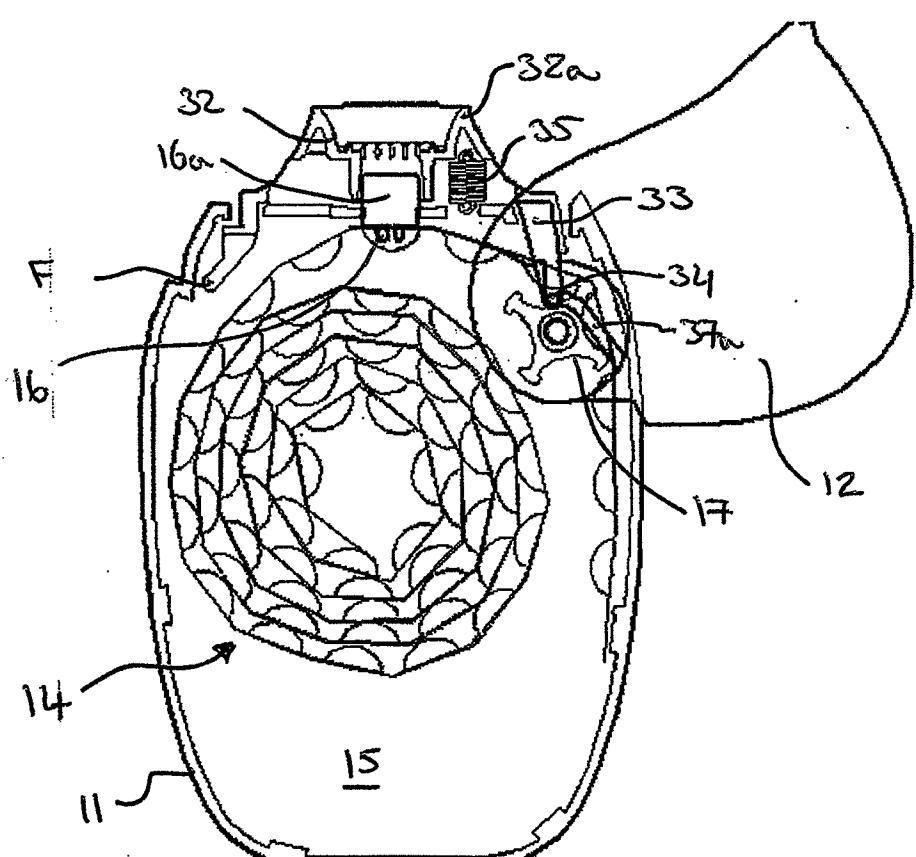


Figure 8

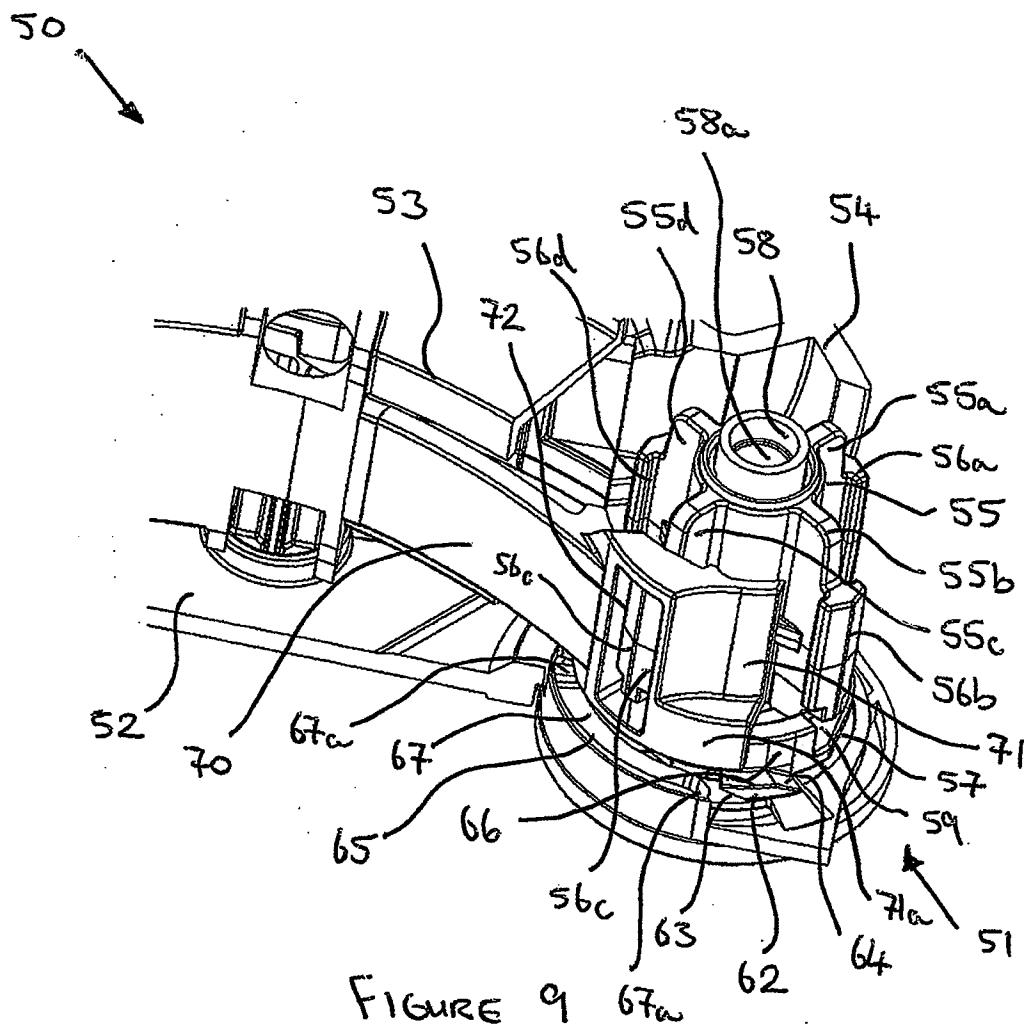
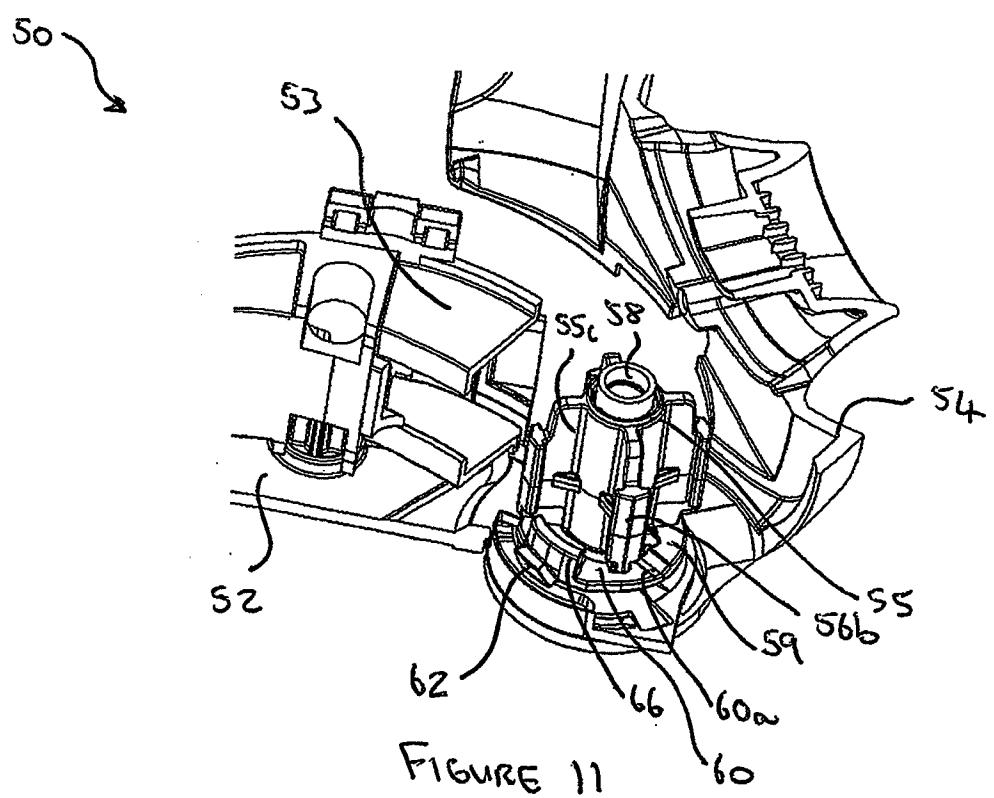
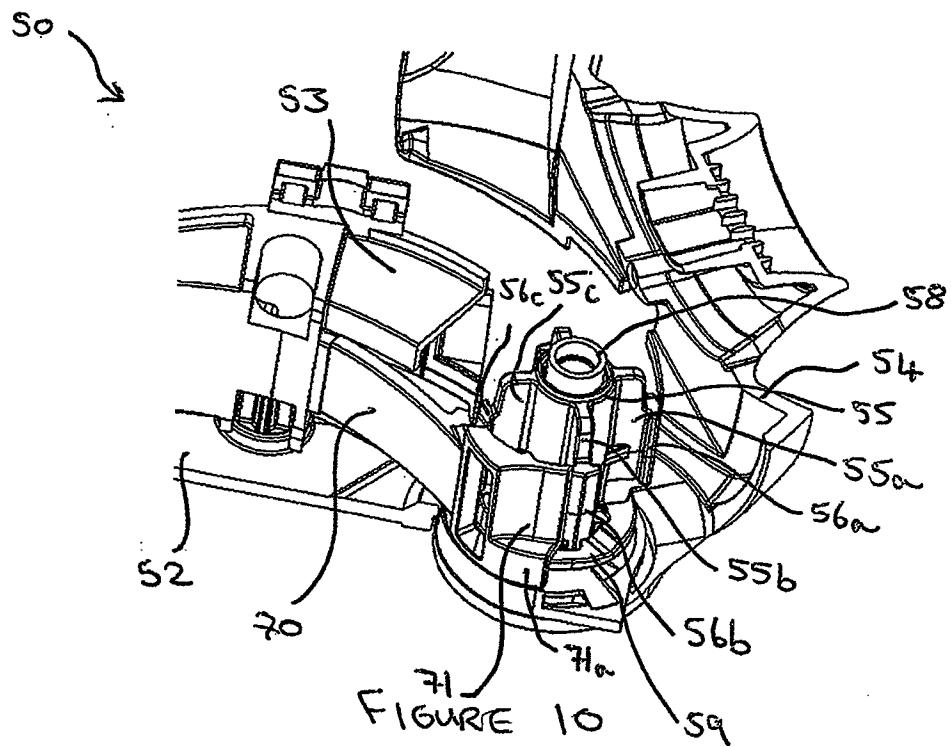


FIGURE 9 67a



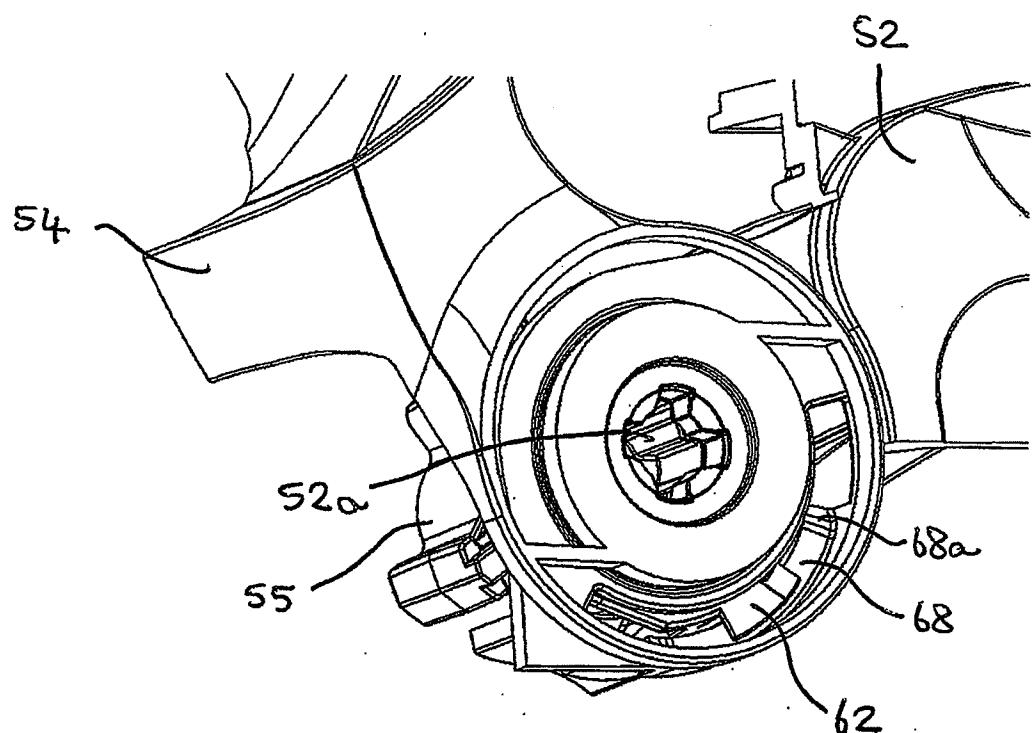
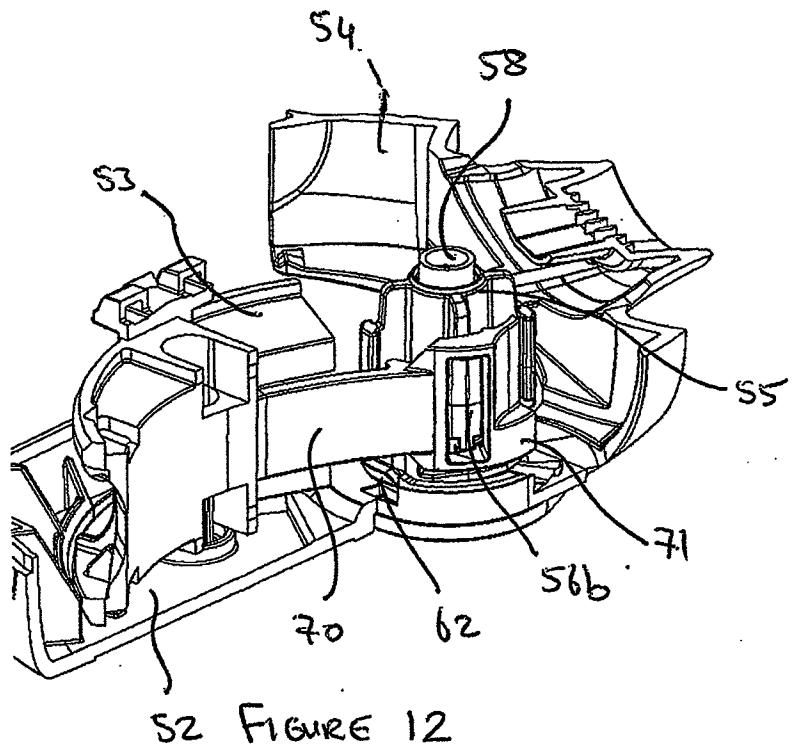


FIGURE 13

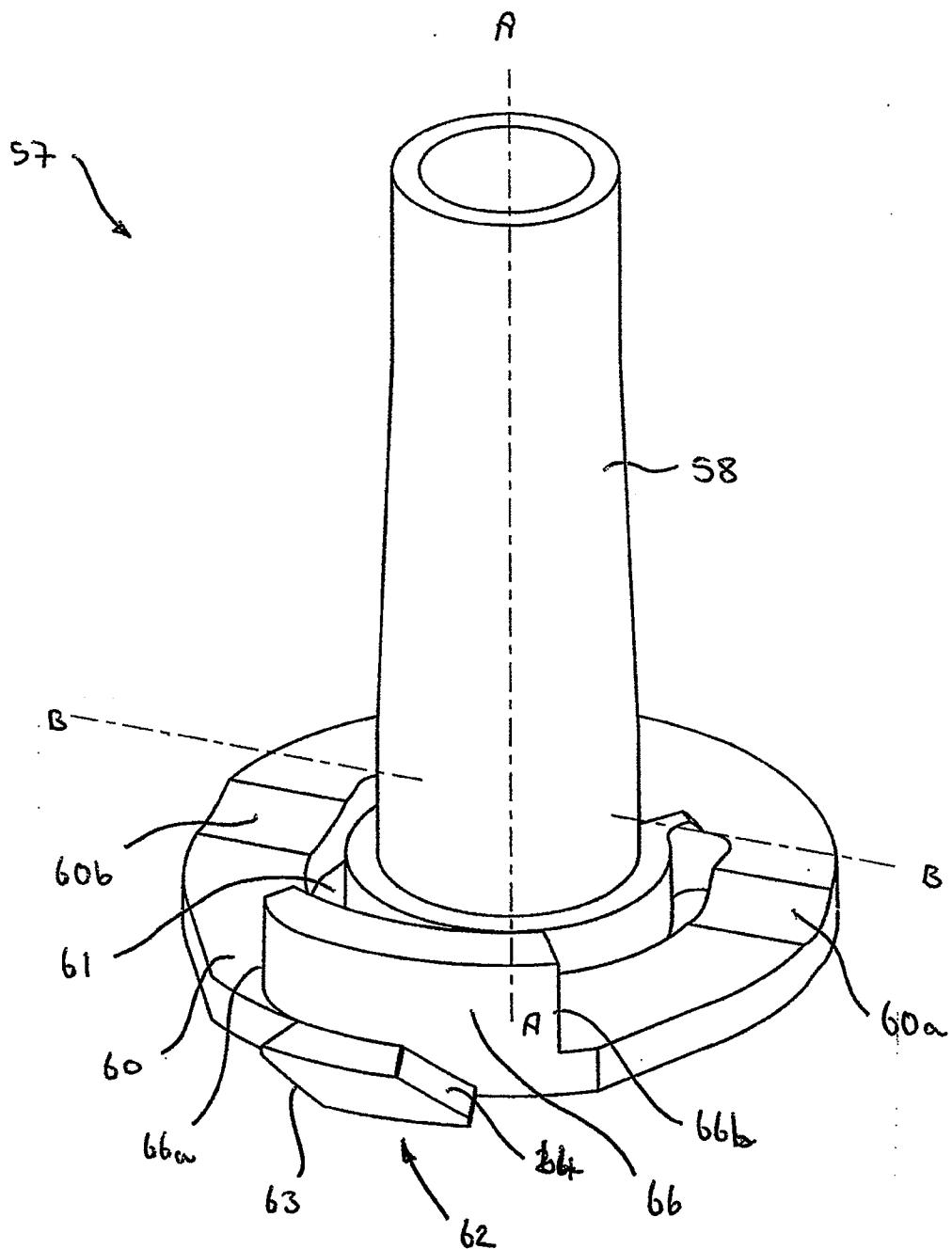


FIGURE 14a

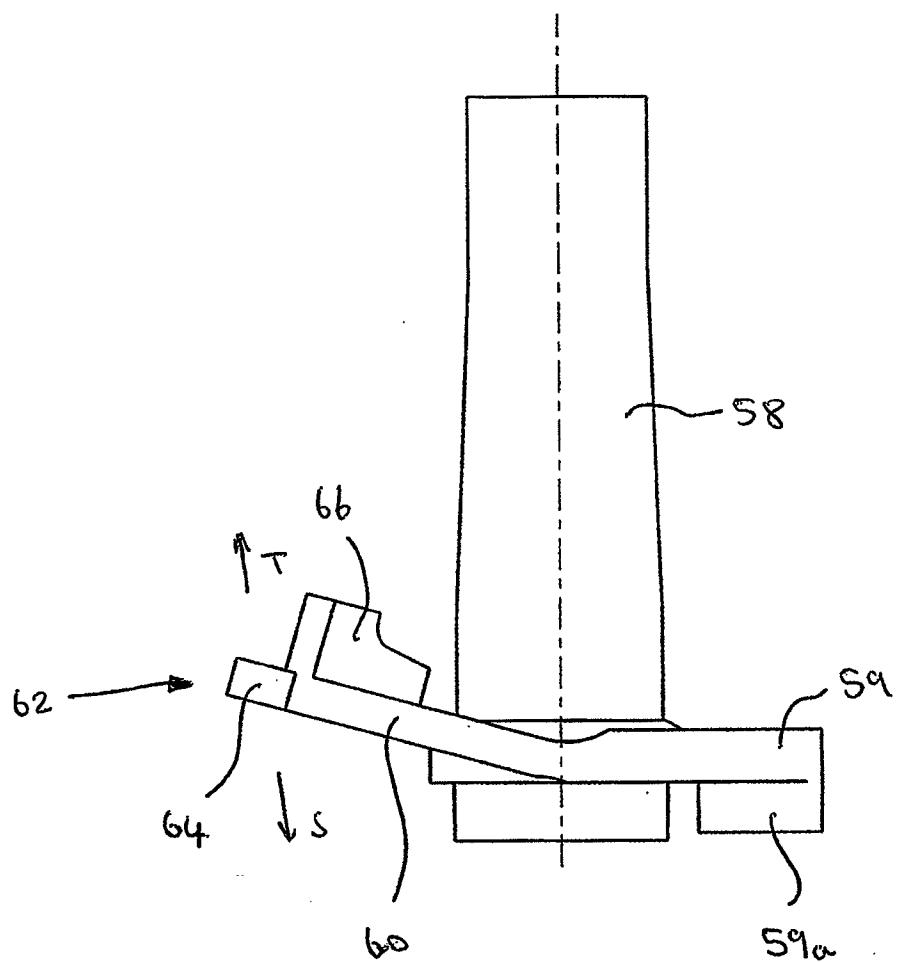


FIGURE 14b.

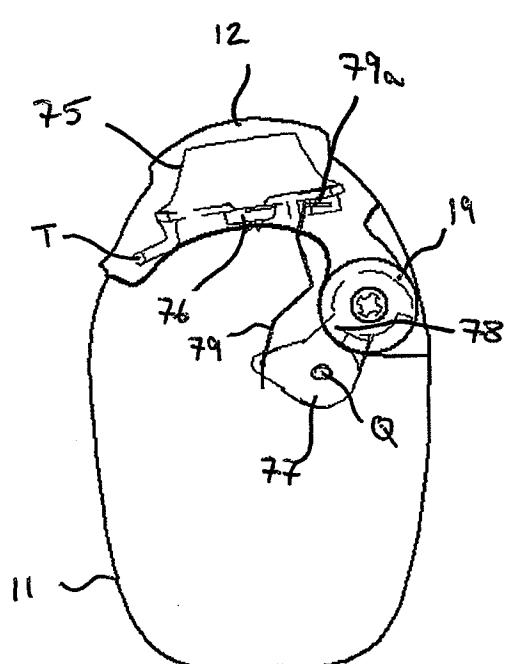


FIGURE 15a

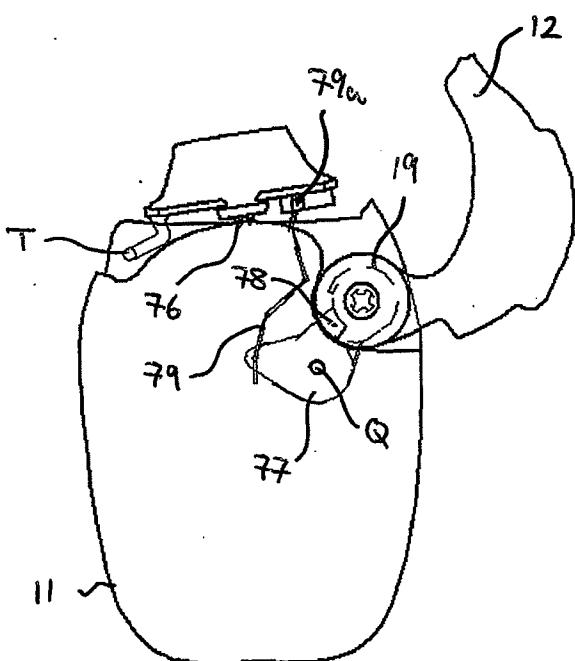


FIGURE 15b

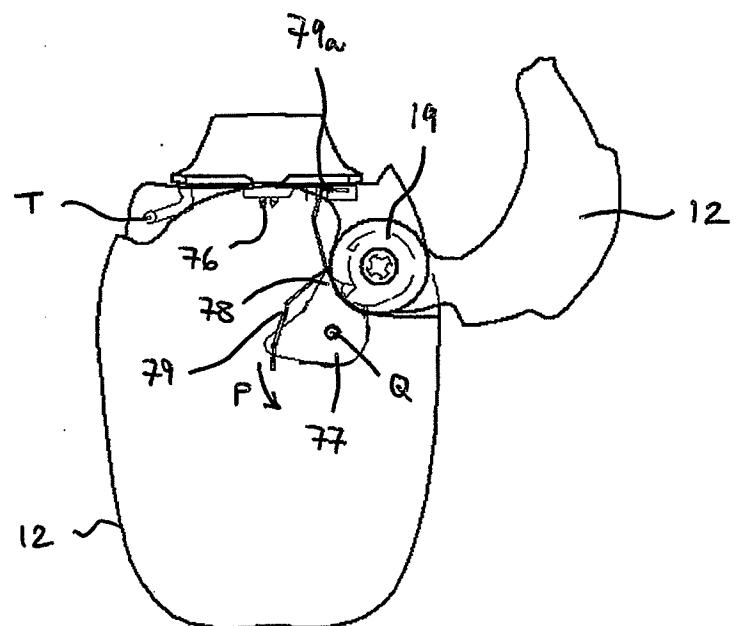


FIGURE 15c

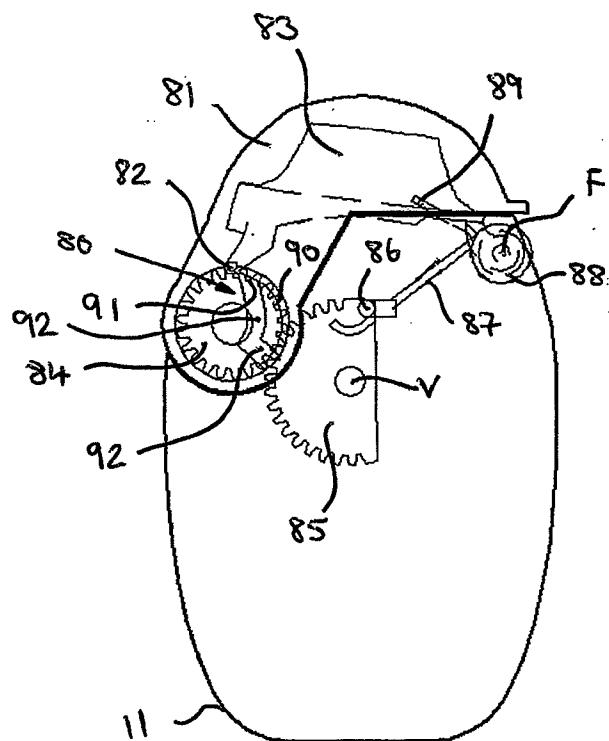


FIGURE 16a

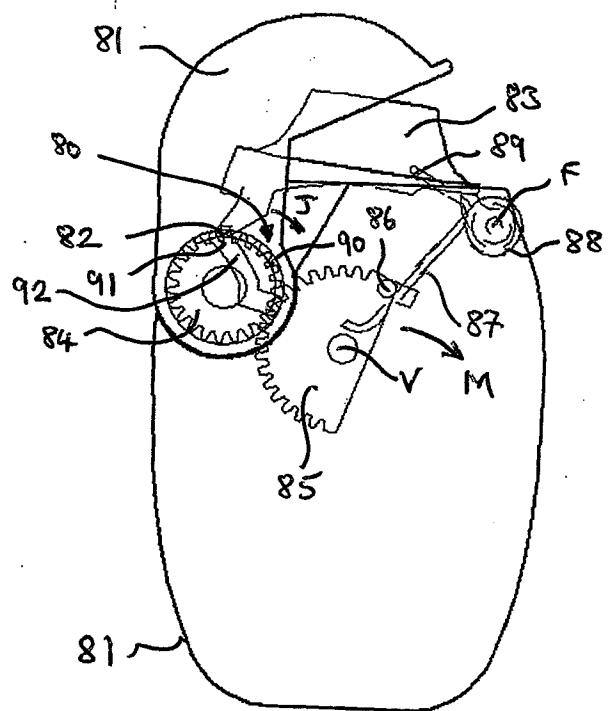


FIGURE 16b

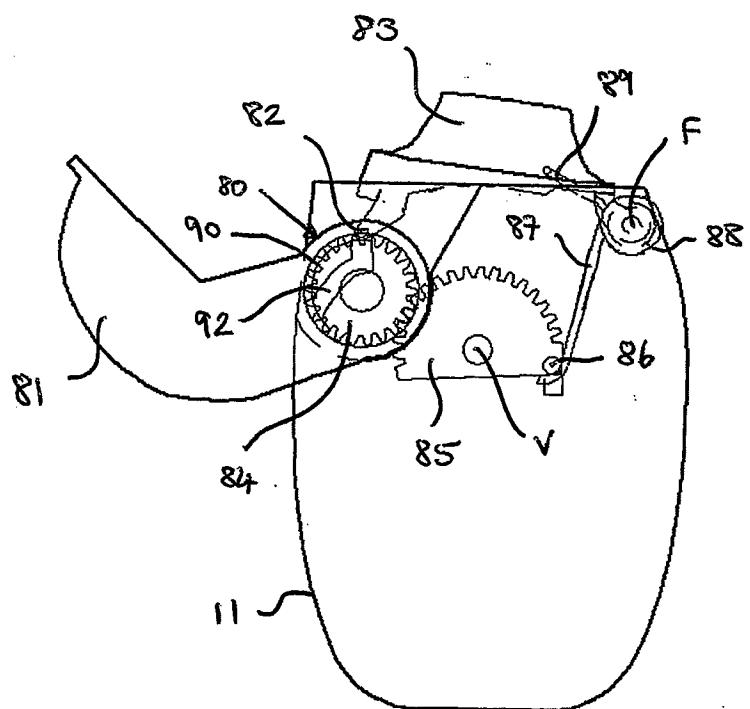


FIGURE 16c

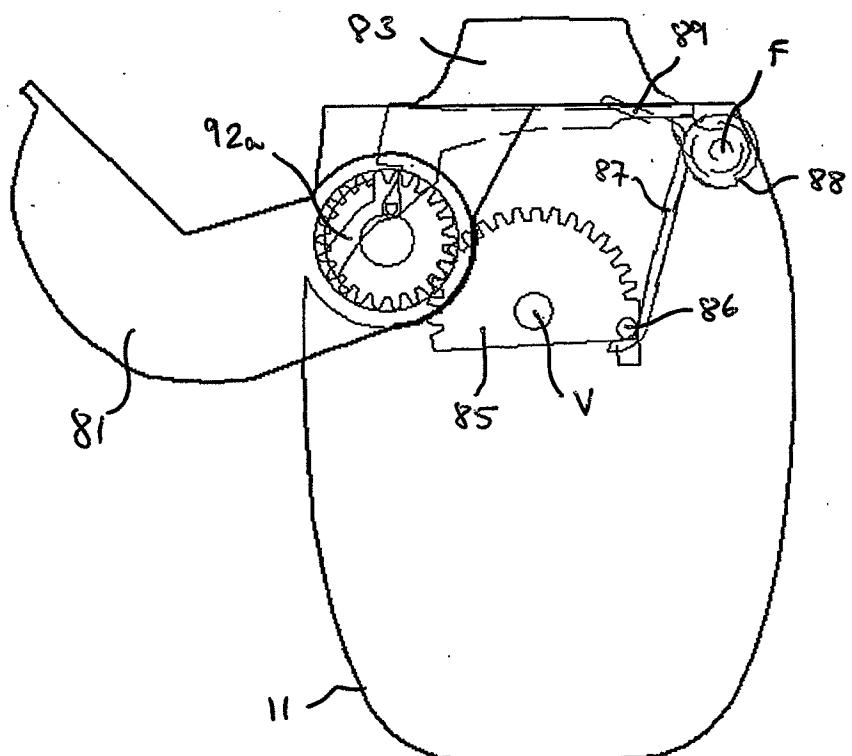


FIGURE 16d

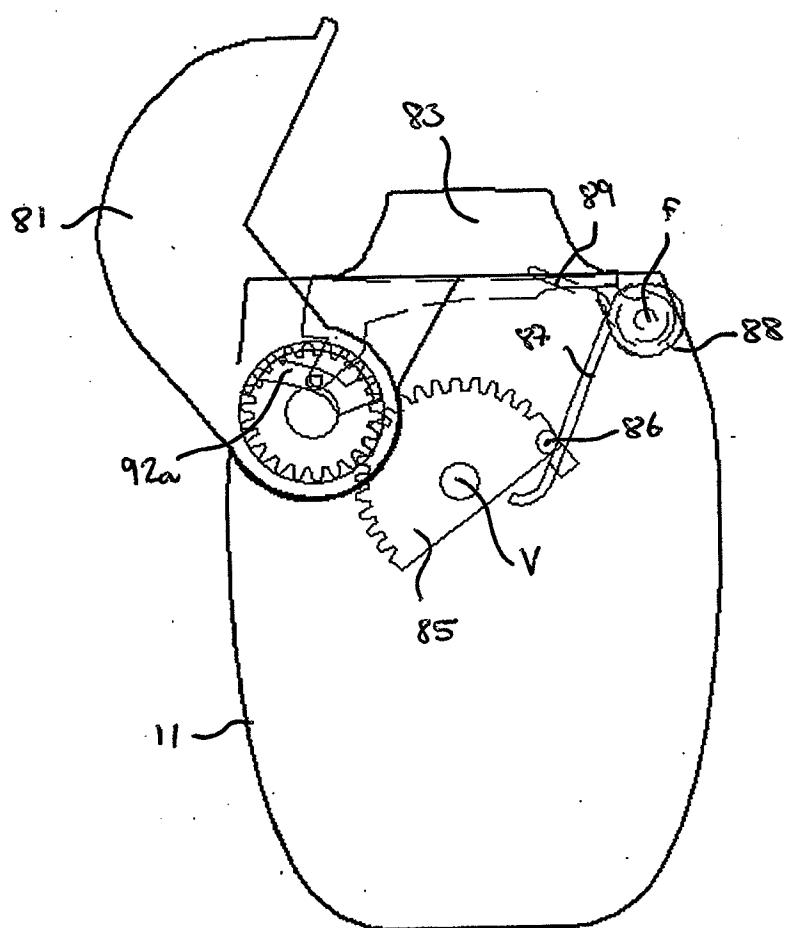


FIGURE 16e

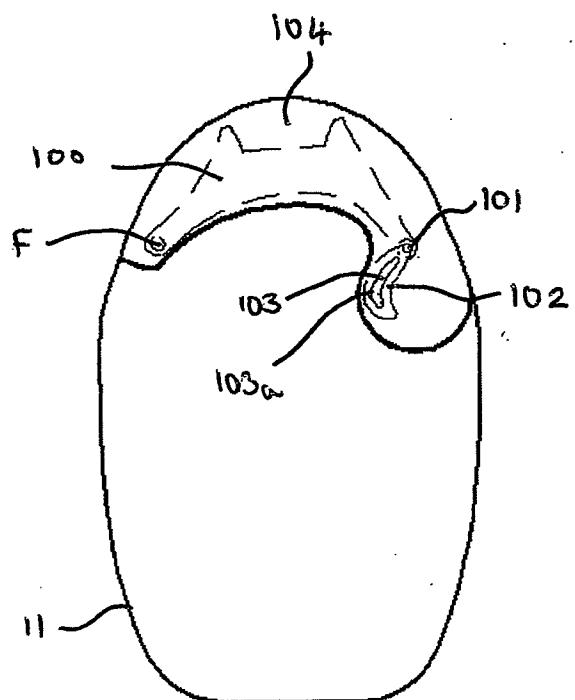


FIGURE 17a

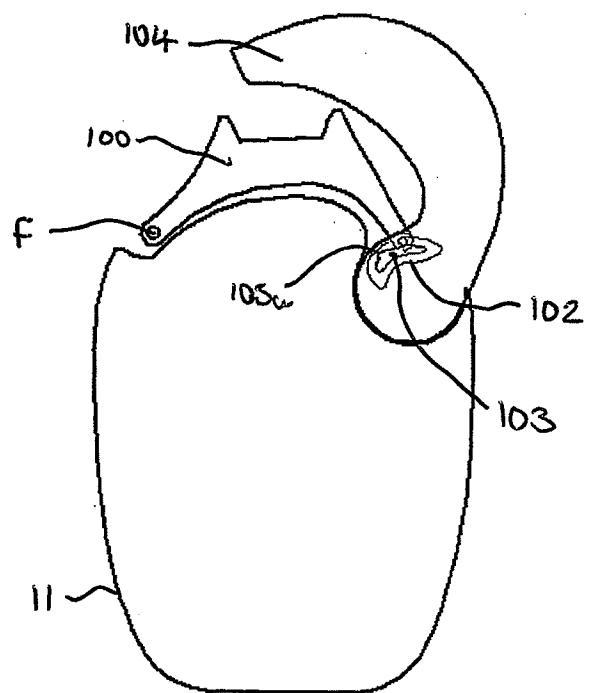


FIGURE 17b

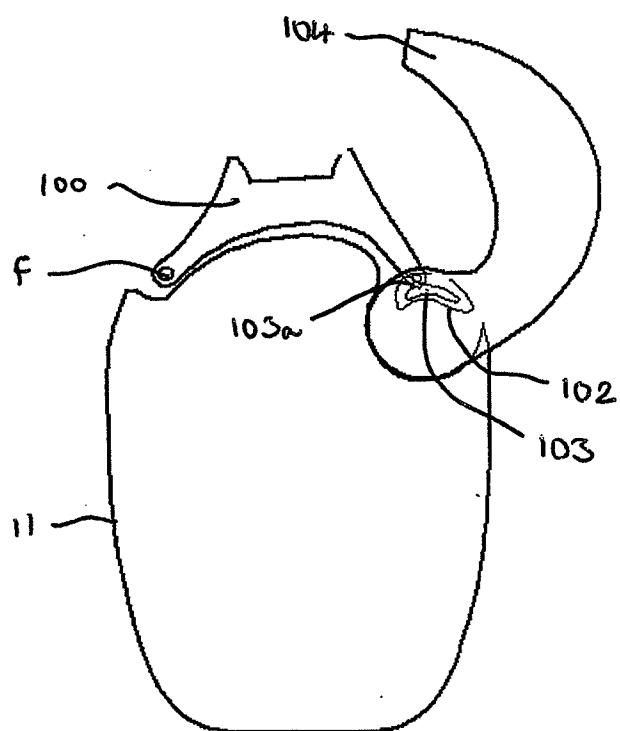


FIGURE 17c

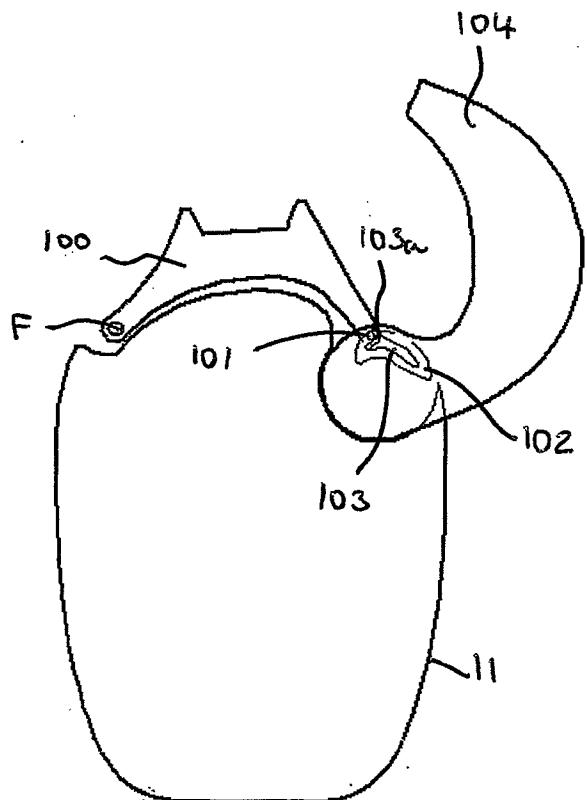


FIGURE 17d

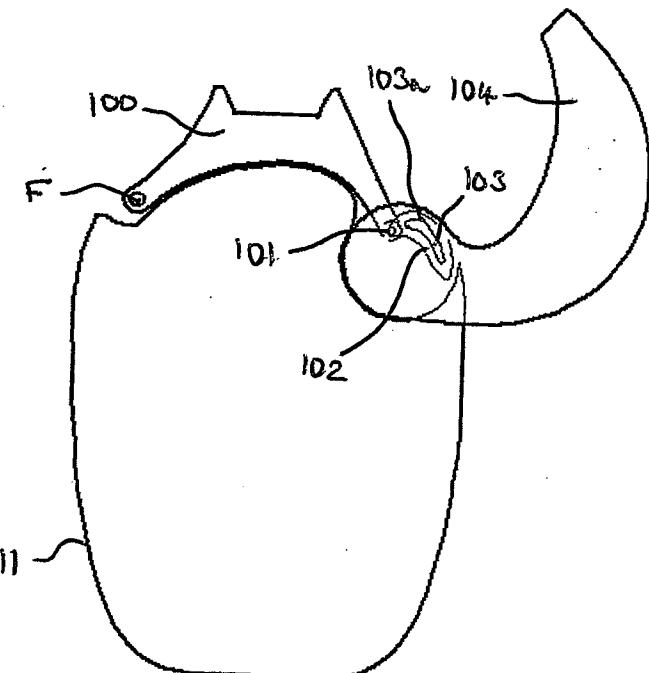


FIGURE 17e

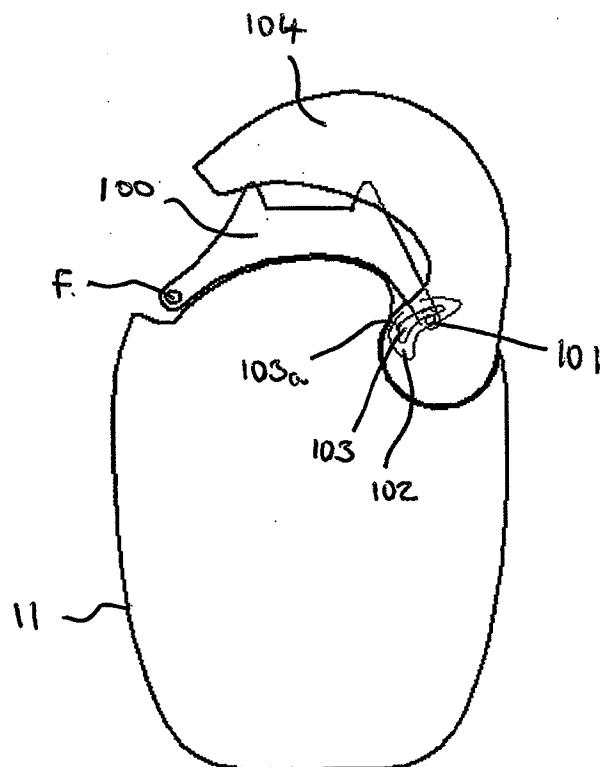


FIGURE 17f

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2009/050733

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 407 042 A (VECTURA LTD) 20 April 2005 (2005-04-20) page 18, line 25 - page 19, line 25; figures 1,11,12 ----- WO 2005/037353 A (VECTURA LTD) 28 April 2005 (2005-04-28) page 25, line 21 - page 27, line 19; figures 11,12,24,25 ----- WO 90/13328 A (RIKER LABORATORIES) 15 November 1990 (1990-11-15) the whole document ----- GB 2 340 758 A (BESPAK PLC) 1 March 2000 (2000-03-01) page 9, line 27 - page 11, line 16; figures 8,9 ----- -/-	1-60 1-60 1-20 1

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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21 April 2009

07/05/2009

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer
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Germano, Alessandro

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/050733

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No  
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