1. *Efficacy*

1.1. *Primary efficacy measure*

Over the first 48 hours after study drug initiation, mean SPID was significantly greater for both doses of HPβCD diclofenac (18.75 mg, p = 0.032; 37.5 mg, p = 0.0001), and for ketorolac (p < 0.0001), than for placebo (see Figure 8). Figure 8 shows the sum of pain intensity differences (SPID) from 0–24 hours and 0–48 hours. Visual analog scale (VAS) pain intensity was assessed at baseline and at specified intervals in the 48 hours subsequent to first drug dose. Pain intensity difference was calculated as the baseline pain intensity minus pain intensity at each scheduled assessment (larger numbers indicate greater pain relief). SPID was shown for the 0-24 and 0-48 hour time periods for placebo, ketorolac 30 mg, diclofenac 18.75 mg, and diclofenac 37.5 mg (error bars indicate standard error (SE)). There were no significant differences in SPID between active treatments. $*p < 0.05$, $**p \leq 0.0001$ v.s. placebo. These results were consistent regardless of baseline pain intensity. There were no statistically significant differences in efficacy between the three active treatment groups.

1.2. *Secondary efficacy measures*

Similar to the 0-48 hour interval, SPID over the 0–24 hour interval was significantly greater than placebo for both HPβCD diclofenac doses (18.75 mg, p = 0.015; 37.5 mg, p < 0.0001) and ketorolac, (p < 0.0001) (Figure 3). For the 0-72 hour period, 18.75 mg diclofenac did not lead to a significantly greater SPID than placebo (p = 0.08), but 37.5 mg diclofenac (p=0.0010) and ketorolac (p=0.0018) did significantly improve SPID. Mean PID was consistently greater with the active treatments than with placebo over the first 45 hours, with the exception of the 6-hour and 30-hour assessments.

The criterion for meaningful pain relief (≥30% reduction) was based on the threshold previously reported as meaningful for acute pain in the postoperative setting. During the first 6-hour dosing period, 55.3% (n=42) of patients receiving placebo had a ≥30% reduction in pain intensity, while 76.8% (n=63) of patients on ketorolac, 64.3% (n=54) of patients on 18.75 mg HPβCD diclofenac, and 69.8% (n=60) of patients on 37.5 mg HPβCD diclofenac reported a ≥30% reduction. The mean time to ≥30% pain intensity reduction among subjects reporting this decline within 6 hours following first study drug dose was rapid across all treatment groups (27-33 minutes for the modified ITT population). Median times to ≥30% pain

WHAT IS CLAIMED IS:

1. A method for treating post-operative pain in a mammal, which method comprises parenterally administering to the mammal in need thereof a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

wherein the post-operative pain results from orthopedic surgery.

2. The method of claim 1, wherein the mammal has a high-risk of an adverse reaction to analgesia.

3. The method of claim 1, wherein the mammal weighs at least about 210 lbs. (95 kg).

4. The method of claim 1, wherein the mammal has hepatic impairment.

5. The method of claim 1, wherein the mammal has renal impairment.

6. The method of claim 1, wherein the mammal is at least about 65 years old.

7. The method of claim 1, wherein the mammal is suffering from moderate to severe pain.

8. The method of claim 1, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

9. The method of claim 1, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

10. The method of claim 1, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

11. The method of claim 1, wherein the method provides pain relief to the mammal within about ten minutes after administration.

12. The method of claim 1, wherein the method further comprises administration of an amount of rescue medication.

13. The method of claim 12, wherein the method reduces the amount of rescue medication by at least about 40% within about 24 hours post-administration.

14. The method of claim 12, wherein the method reduces the amount of rescue medication by at least about 40% within about 48 hours post-administration.

15. The method of claim 12, wherein the method reduces the amount of rescue medication by at least about 40% within about 72 hours post-administration.

16. The method of claim 12, wherein the method reduces the amount of rescue medication by at least about 40% within about 96 hours post-administration.

17. The method of claim 12, wherein the method reduces the amount of rescue medication by at least about 40% within about 120 hours post-administration.

18. The method of claim 1, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

19. A method for treating post-operative pain in a mammal, which method comprises parenterally administering to the mammal in need thereof a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

wherein the post-operative pain results from abdominal or pelvic surgery.

20. The method of claim 19, wherein the mammal weighs at least about 210 lbs. (95 kg).

21. The method of claim 19, wherein the mammal has hepatic impairment.

22. The method of claim 19, wherein the mammal has renal impairment.

23. The method of claim 19, wherein the mammal is at least about 65 years old.

24. The method of claim 19, wherein the mammal is suffering from moderate to severe pain.

25. The method of claim 19, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

26. The method of claim 19, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

27. The method of claim 19, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

28. The method of claim 19, wherein the method provides at least about a 30% reduction of pain intensity at about 45 minutes post-administration.

29. The method of claim 19, wherein the method further comprises administration of an amount of rescue medication.

30. The method of claim 29, wherein the method reduces the amount of rescue medication by at least about 35% within about 24 hours post-administration.

31. The method of claim 29, wherein the method reduces the amount of rescue medication by at least about 35% within about 48 hours post-administration.

32. The method of claim 19, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

33. A method for treating pain in a mammal, which method comprises parenterally administering to the mammal in need thereof a pharmaceutical composition comprising:

a. about 37.5 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

wherein the pain results from cancer.

34. The method of claim 33, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

1. *Efficacy*

1.1. *Primary efficacy measure*

Over the first 48 hours after study drug initiation, mean SPID was significantly greater for both doses of HPβCD diclofenac (18.75 mg, p = 0.032; 37.5 mg, p = 0.0001), and for ketorolac (p < 0.0001), than for placebo (see Figure 8). Figure 8 shows the sum of pain intensity differences (SPID) from 0–24 hours and 0–48 hours. Visual analog scale (VAS) pain intensity was assessed at baseline and at specified intervals in the 48 hours subsequent to first drug dose. Pain intensity difference was calculated as the baseline pain intensity minus pain intensity at each scheduled assessment (larger numbers indicate greater pain relief). SPID was shown for the 0-24 and 0-48 hour time periods for placebo, ketorolac 30 mg, diclofenac 18.75 mg, and diclofenac 37.5 mg (error bars indicate standard error (SE)). There were no significant differences in SPID between active treatments. $*p < 0.05$, $**p \leq 0.0001$ v.s. placebo. These results were consistent regardless of baseline pain intensity. There were no statistically significant differences in efficacy between the three active treatment groups.

1.2. *Secondary efficacy measures*

Similar to the 0-48 hour interval, SPID over the 0–24 hour interval was significantly greater than placebo for both HPβCD diclofenac doses (18.75 mg, p = 0.015; 37.5 mg, p < 0.0001) and ketorolac, (p < 0.0001) (Figure 8). For the 0-72 hour period, 18.75 mg diclofenac did not lead to a significantly greater SPID than placebo (p = 0.08), but 37.5 mg diclofenac (p=0.0010) and ketorolac (p=0.0018) did significantly improve SPID. Mean PID was consistently greater with the active treatments than with placebo over the first 45 hours, with the exception of the 6-hour and 30-hour assessments.

The criterion for meaningful pain relief (≥30% reduction) was based on the threshold previously reported as meaningful for acute pain in the postoperative setting. During the first 6-hour dosing period, 55.3% (n=42) of patients receiving placebo had a ≥30% reduction in pain intensity, while 76.8% (n=63) of patients on ketorolac, 64.3% (n=54) of patients on 18.75 mg HPβCD diclofenac, and 69.8% (n=60) of patients on 37.5 mg HPβCD diclofenac reported a ≥30% reduction. The mean time to ≥30% pain intensity reduction among subjects reporting this decline within 6 hours following first study drug dose was rapid across all treatment groups (27-33 minutes for the modified ITT population). Median times to ≥30% pain

WHAT IS CLAIMED IS:

1. The use of a pharmaceutical composition comprising:
   a. about 50 mg or less of a diclofenac compound; and
   b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain, wherein the post-operative pain results from orthopedic surgery.

2. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 1, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

3. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 1, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

4. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 1, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

5. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 1, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

6. The use of a pharmaceutical composition comprising:
   a. about 50 mg or less of a diclofenac compound; and
   b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain, wherein the post-operative pain results from abdominal or pelvic surgery.

7. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 6, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

8. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 6, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

9. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 6, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

10. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 6, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

11. The use of a pharmaceutical composition comprising:

a. about 37.5 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of pain, wherein the pain results from cancer.

12. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 11, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

13. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal, wherein the post-operative pain results from orthopedic surgery.

14. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal having a high-risk of an adverse reaction to analgesia, wherein the post-operative pain results from orthopedic surgery.

15. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in a manufacture of a medicament for the treatment of post-operative pain in a mammal weighing at least about 210 lbs. (95 kg), wherein the post-operative pain results from orthopedic surgery.

16. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal having hepatic impairment, wherein the post-operative pain results from orthopedic surgery.

17. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal having renal impairment, wherein the post-operative pain results from orthopedic surgery.

18. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal of at least about 65 years old, wherein the post-operative pain results from orthopedic surgery.

19. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal suffering from moderate to severe pain, wherein the post-operative pain results from orthopedic surgery.

20. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 13, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

21. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 13, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

22. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 13, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

23. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 13, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

24. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal, wherein the post-operative pain results from abdominal or pelvic surgery.

25. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal weighing at least about 210 lbs. (95 kg), wherein the post-operative pain results from abdominal or pelvic surgery.

26. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal having hepatic impairment, wherein the post-operative pain results from abdominal or pelvic surgery.

27. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal having renal impairment, wherein the post-operative pain results from abdominal or pelvic surgery.

28. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal of at least about 65 years old, wherein the post-operative pain results from abdominal or pelvic surgery.

29. The use of a pharmaceutical composition comprising:

a. about 50 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of post-operative pain in a mammal suffering from moderate to severe pain, wherein the post-operative pain results from abdominal or pelvic surgery.

30. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 24, wherein the pharmaceutical composition comprises about 37.5 mg or less of diclofenac compound.

31. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 24, wherein the pharmaceutical composition comprises about 18.75 mg or less of diclofenac compound.

32. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 24, wherein the pharmaceutical composition comprises about 9.375 mg or less of diclofenac compound.

33. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 24, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).

34. The use of a pharmaceutical composition comprising:

a. about 37.5 mg or less of a diclofenac compound; and

b. a beta-cyclodextrin compound;

in the manufacture of a medicament for the treatment of pain in a mammal, wherein the pain results from cancer.

35. The use of the pharmaceutical composition in the manufacture of a medicament as claimed in claim 34, wherein the beta-cyclodextrin compound is hydroxypropyl-beta-cyclodextrin (HPβCD).