F. No. 04-146/2007-DC
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(FDC Division)

FDA Bhawan, Kotla road,
New Delhi
Dated: 12 APR 2019

To

All State/UT Drugs Controller

Subject:- **Consideration of the directions of Hon'ble Supreme Court of India in the case of 294 FDCs-reg.**

Sir,

Please refer to this Directorate letters dated 12.12.2018 on the subject mentioned above whereby you were requested to direct all the concerned manufacturers to submit information/data to this office so that further action can be taken on these FDCs (copies enclosed).

It may be informed that this office has received only a few applications in this regard. You are therefore once again requested to direct all the concerned manufacturers of the 49 FDCs as well as 17 FDCs under your jurisdiction as mentioned in this office letters dated 12.12.2018 to submit the requisite data/information on these FDCs by 30.06.2019.

Further, the manufacturers of these FDCs may also be informed that in case of non-submission of data/information by 30.06.2019, this Directorate reserves the right to make its decision on the basis of information available before it in light of the judgement of the Hon'ble supreme Court.

Yours faithfully,

(Dr. S. Eswara Reddy)
Drugs Controller General (India)

Encl: 2 letters dated 12.12.2018

**Copy for information and necessary action to:-**

1. Web site of CDSCO.
2. CDSCO Zonal and Sub-Zonal offices.
3. All Drugs Manufacturer Association with the request to publicise it widely amongst their members for submitting the data.

F. No. 04-146/2007-DC
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(FDC Division)

FDA Bhawan, Kotla road,
New Delhi
Dated: 12 DEC 2018

To

All State/UT Drugs Controllers

Subject:- **Consideration of the directions of Hon'ble Supreme Court of India in the case of 294 FDCs in respect of FDCs which require further generation of data –reg.**

Sir,

The office of Drugs Controller General (India) received complaints from Consumer Associations in year 2007 regarding Fixed Dose Combinations (FDC) not approved by DCG(I) but marketed in the country. As a part of follow up action of complaints, the office of DCG(I) prepared a list of 294 FDCs and directions were issued to all State/UT Drugs Controllers to withdraw these 294 FDCs which were licensed without approval of DCG(I). The manufacturers association, however, got stay from the Hon'ble High Court of Madras on the directions issued in the matter.

The matter was then placed in DTAB in the 56th meeting dated 16.01.2008. A Sub-Committee was constituted by DTAB to examine these FDCs. Accordingly the Sub-Committee examined these FDCs and submitted its report to the DTAB. DTAB in its meeting held on 16.02.2015 agreed with the recommendations of Sub-Committee of DTAB. The Hon'ble Supreme Court as per its judgement dated 15.12.2017 has accepted the recommendations of DTAB.

As per the recommendations of DTAB, there are 49 FDCs which require further generation of data in terms of safety and efficacy by conducting clinical trial. The details of these 49 FDCs along with the detailed recommendations of DTAB Sub-Committee are annexed herewith as **Annexure A**.

You are requested to direct all concerned manufacturers of the above mentioned 49 FDCs under your jurisdiction to submit the Clinical Trial protocol/PMS data for obtaining NOC from this Directorate for further generation of data in terms of safety and efficacy as mentioned under **Annexure A**, so that final action can be taken on these FDCs. The study protocols are required to be submitted in hard copy as well as soft copy(i.e. in CD form) **latest by 01.04.2019.**

It may be communicated that in case of non-submission, this Directorate reserves the right to make its decision on the basis of information available before it in light of the judgement of the Hon'ble Supreme Court.

Yours faithfully.

(Dr. S. Eswara Reddy)
Drugs Controller General (India)

Copy for information and necessary action to:-

1. Web site of CDSCO.
2. CDSCO Zonal and Sub-Zonal offices.
3. All Drugs manufacturer association with the request to publicise it widely amongst their members for submitting the protocol.

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 1 | Aceclofenac+ Paracetamol+ Chlorzoxazone | Committee observed that there are no published data on safety and efficacy of the above mentioned FDCs. Further, muscle reluxant like Chlorzoxazone is generally given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Clinical opinion was sought from the clinicians attending the meeting. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Chlorzoxazone + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs . |
| 2 | Aceclofenac+ Paracetamol+ Serratiopeptidase | 3 drug combination of Serratiopeptidase + Paracetamol + Aceclofenac / Diclofenac / Ibuprofen / Nimesulide needs to be demonstrated to be superior in efficacy than Serratiopeptidase/NSAID + Paracetamol (2 drug FDC). Since the published data on efficacy of 3 drug FDCs are not available clinical opinion was sought from the clinicians attending the meeting. Although the clinicians especially the practicing Orthopedic surgeons supported the usefulness of serratiopeptidase, it was concluded that documented evidence complementing the positive clinical experience is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute pain subject to condition that clinical trial data needs to be generated in adequately powered study comparing 3 drug FDC with 2-drug combination of Serratiopeptidase/NSAID+ Paracetamol within one year from the date of final decision on marketing of these FDCs .<br><br>Further, Dr Y K Gupta and Dr Nilima Kshirsagar suggested that for serratiopeptidase there needs to be data available substantiating its absorption. This could be in form of documented evidence, and in absence of same, the industry has to conduct a study to prove that orally administered |
| 3 | Aceclofenac+ Paracetamol+ Tizanidine | Committee observed that there are no published data on safety and efficacy. Further, muscle reluxant Tizanidine is given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Tizanidine + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs. |
| 4 | Aceclofenac+ Paracetamol+ Tramadol | Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that this FDCs can be considered only for short term use in acute pain subject to condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Aceclofenac + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs. |
| 5 | Alprazolam+ Melatonin | The committee observed that FDC of Alprazolam + Melatonin (S. No. 31 as per DCG(I) List)is for the treatment of insomnia. However, there is no rationality and scientific evidence available in support of the formulation. The specialist Dr. Deshpende, (Psychiatrist) from RML Hospital, New Delhi stated that the combination is not rational for treatment of insomnia/sleep disorders as alprazolam is anxiolytic drug and it is not used for treatment of insomnia/sleep disorders. Dr Rehan, also agreed with the opinion of Dr. Deshpande since the evidence are not adequate.<br>After detailed deliberation the committee opined that clinical trial may be carried out to prove that the combination is useful in withdrawal of benzodiazepine and also to prove that the combination is useful in treatment of chronic insomnia. |
| 6 | Alprazolam+ Propranolol | The committee opined that the FDCs may be considered only for acute anxiety disorders. However pharmacokinetics study is required to be carried out to prove that there is no drug-drug interaction between the individual drugs in the formulation before considering it for the said indication. |
| 7 | Amoxicillin+ Cloxacillin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 8 | Amoxicillin+ Serratiopeptidase+ Lactobacillus Sporogenes | The above FDCs were discussed on following lines:<br>1. Whether Serratiopeptidase is absorbed when taken orally?<br>2. Serratiopeptidase is an enzyme which is known to be degraded in gastrointestinal tract.<br><br>However, one report published in 1994 by Moriya N et al. in Biotechnol Appl Biochem 1994 Aug;20(Pt1):101-8 titled "Intestinal absorption of Serratiopeptidase (TSP) in rats" indicates that orally administered TSP was absorbed from the intestinal tract and transferred into the circulation in an enzymically active form. However, the cautionary note in this study is that this study was conducted in rats and no active absorption has been demonstrated in humans.<br><br>An article published in 1986 by Koyama A et al. in Jpn J Antibiot. 1986 Mar; 39(3):761-71 titled "Augmentation by serrapeptase of tissue permeation by cefotiam" shows that there is an improved penetration of cephalosporin into the tissues. In spite of this, there is no evidence of superiority of the FDC over Amoxicillin when used alone. Therefore, there is insufficient evidence for adding Serratiopeptidase to antibiotic. Committee opined that above formulations shall not be permitted unless clinical evidence is generated. |
| 9 | Amoxycillin+ Clavulanic acid+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 10 | Amoxycillin+ Cloxacillin+ Lactic acid bacillus+ Serrapeptase | The above FDCs were discussed on following lines:<br>1. Whether Serratiopeptidase is absorbed when taken orally?<br>2. Serratiopeptidase is an enzyme which is known to be degraded in gastrointestinal tract.<br><br>However, one report published in 1994 by Moriya N et al. in Biotechnol Appl Biochem 1994 Aug;20(Pt1):101-8 titled "Intestinal absorption of Serratiopeptidase (TSP) in rats" indicates that orally administered TSP was absorbed from the intestinal tract and transferred into the circulation in an enzymically active form. However, the cautionary note in this study is that this study was conducted in rats and no active absorption has been demonstrated in humans.<br><br>An article published in 1986 by Koyama A et al. in Jpn J Antibiot. 1986 Mar; 39(3):761-71 titled "Augmentation by serrapeptase of tissue permeation by cefotiam" shows that there is an improved penetration of cephalosporin into the tissues. In spite of this, there is no evidence of superiority of the FDC over Amoxicillin when used alone. Therefore, there is insufficient evidence for adding Serratiopeptidase to antibiotic. Committee opined that above formulations shall not be permitted |
| 11 | Amoxycillin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 12 | Amoxycillin+ Lactobacillus acidophilus+ Flucloxacillin Sodium | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 13 | Amoxycillin+ Serratiopeptidase | The above FDCs were discussed on following lines:<br>1. Whether Serratiopeptidase is absorbed when taken orally?<br>2. Serratiopeptidase is an enzyme which is known to be degraded in gastrointestinal tract.<br><br>However, one report published in 1994 by Moriya N et al. in Biotechnol Appl Biochem 1994 Aug;20(Pt1):101-8 titled "Intestinal absorption of Serratiopeptidase (TSP) in rats" indicates that orally administered TSP was absorbed from the intestinal tract and transferred into the circulation in an enzymically active form. However, the cautionary note in this study is that this study was conducted in rats and no active absorption has been demonstrated in humans.<br><br>An article published in 1986 by Koyama A et al. in Jpn J Antibiot. 1986 Mar; 39(3):761-71 titled "Augmentation by serrapeptase of tissue permeation by cefotiam" shows that there is an improved penetration of cephalosporin into the tissues. In spite of this, there is no evidence of superiority of the FDC over Amoxicillin when used alone. Therefore, there is insufficient evidence for adding Serratiopeptidase to antibiotic. Committee opined that above formulations shall not be permitted |

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 14 | Ampicillin+ Cloxacillin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 15 | Ampicillin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 16 | Calcium dobesilate+ Decusate sodium | Dr. S. K. Acharya, the expert from AIIMS, New Delhi opined that there is no documented evidence in support of safety and efficacy for these combination products. After detailed deliberation, committee recommended that well designed clinical trials in adequate number of patients need to be conducted. Clinical trial protocol should be developed in consultation with the experts. |
| 17 | Calcium dobesilate+ Lignocaine | Dr. S. K. Acharya, the expert from AIIMS, New Delhi opined that there is no documented evidence in support of safety and efficacy for these combination products. After detailed deliberation, committee recommended that well designed clinical trials in adequate number of patients need to be conducted. Clinical trial protocol should be developed in consultation with the experts. |
| 18 | Calcium dobesilate+ Lignocaine+ Hydrocortisone | This is a three drug combination with specific indication for symptomatic relief from painful itching hemorrhoids and inflammation. There is only one study available w.r.t. local application of calcium Dobesilate in symptomatic relief of hemorrhoids. Calcium Dobesilate for oral has been approved by DCG(I) however the topical use of Calcium Dobesilate is not approved. There is no published study also for safety and efficacy of Calcium Dobesilate + Lignocaine + Hydrocortisone. FDC is not approved anywhere except Ethiopia. However, there is one study where the 3 drug combination is available with dexamethasone which is also a steroid and is published in journal GEN 1995; 49(4) 296-302. The traceability of journal as on date could not be identified. Although the journal is pub med indexed, however the full form of the journal could not be traced. This study is on 40 subjects, which is inadequate. The study results shows 2 arms study, one arm with calcium Dobesilate and other without calcium Dobesilate and it had no significant difference (i.e. 88% vs. 85.5% only). The concluding line of abstract available says that both the formulation were innocuous.<br><br>With the above information the committee felt that the<br>1. Calcium Dobesilate is not approved as topical by DCG(I)<br>2. There is no evidence of increase enhanced efficacy by addition of Calcium Dobesilate<br>3. The only study available is inadequate to arrive at a statistical significance.<br>Therefore, there is no significant evidence to justify the rationality of the FDC and hence a properly designed Clinical Trial is required in a statistical significant number of subjects. |
| 19 | Calcium Dobesilate+ Troxerutin | Dr. S. K. Acharya, the expert from AIIMS, New Delhi opined that there is no documented evidence in support of safety and efficacy for these combination products. After detailed deliberation, committee recommended that well designed clinical trials in adequate number of patients need to be conducted. Clinical trial protocol should be developed in consultation with the experts. |
| 20 | Cefadroxyl+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 21 | Cefadroxyl+ Probenecid | The committee discussed at length for the benefits of Probenecid with Cephalosporins and also noted from literature that this combination can reduce dose of Probenecid if combined with Cephalosporins. Probenecid has many side effects like kidney stones, polyuria etc.<br>The committee opined that this FDC is rational, however a good scientific pharmacokinetic study must be done to find out dose determination for Probenecid + Cephalosporins in infections where it is indicated for skin and soft tissue infection, UTI, URTI since the dose titration & subsequent reduction is also of equal importance. |

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 22 | Cefdinir+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 23 | Cefixime+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 24 | Cefixime+ Lactobacillus+ Dicloxacillin | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 25 | Cefpodoxime prozetil+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 26 | Cefpodoxime+ Cloxacillin+ Lactobacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 27 | Cefprozil+ Lactobacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 28 | Cefuroxime+ Serratiopeptidase | The above FDCs were discussed on following lines:<br>1. Whether Serratiopeptidase is absorbed when taken orally?<br>2. Serratiopeptidase is an enzyme which is known to be degraded in gastrointestinal tract.<br><br>However, one report published in 1994 by Moriya N et al. in Biotechnol Appl Biochem 1994 Aug;20(Pt1):101-8 titled "Intestinal absorption of Serratiopeptidase (TSP) in rats" indicates that orally administered TSP was absorbed from the intestinal tract and transferred into the circulation in an enzymically active form. However, the cautionary note in this study is that this study was conducted in rats and no active absorption has been demonstrated in humans.<br><br>An article published in 1986 by Koyama A et al. in Jpn J Antibiot. 1986 Mar; 39(3):761-71 titled "Augmentation by serrapeptase of tissue permeation by cefotiam" shows that there is an improved penetration of cephalosporin into the tissues. In spite of this, there is no evidence of superiority of the FDC over Amoxicillin when used alone. Therefore, there is insufficient evidence for adding Serratiopeptidase to antibiotic. Committee opined that above formulations shall not be permitted |
| 29 | Cepodoxime+ Cloxacillin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 30 | Chlorzoxazone+ Paracetamol + Diclofenac | Committee observed that there are no published data on safety and efficacy of the above mentioned FDCs. Further, muscle reluxant like Chlorzoxazone is generally given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Clinical opinion was sought from the clinicians attending the meeting. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Chlorzoxazone + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs . |
| 31 | Chlorzoxazone+ Paracetamol+ Ibuprofen | Committee observed that there are no published data on safety and efficacy of the above mentioned FDCs. Further, muscle reluxant like Chlorzoxazone is generally given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Clinical opinion was sought from the clinicians attending the meeting. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Chlorzoxazone + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs . |
| 32 | Chlorzoxazone+ Paracetamol+ Nimesulide | Committee observed that there are no published data on safety and efficacy of the above mentioned FDCs. Further, muscle reluxant like Chlorzoxazone is generally given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Clinical opinion was sought from the clinicians attending the meeting. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Chlorzoxazone + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs. Additional study to establish hepatic safety needs to be done within six months from the date of final decision on marketing of this FDC since all the 3 ingredients are potentially hepatotoxic. |
| 33 | Diclofenac+ Paracetamol+ Serratiopeptidase | 3 drug combination of Serratiopeptidase + Paracetamol + Aceclofenac / Diclofenac / Ibuprofen / Nimesulide needs to be demonstrated to be superior in efficacy than Serratiopeptidase/NSAID + Paracetamol (2 drug FDC). Since the published data on efficacy of 3 drug FDCs are not available clinical opinion was sought from the clinicians attending the meeting. Although the clinicians especially the practicing Orthopedic surgeons supported the usefulness of serratiopeptidase, it was concluded that documented evidence complementing the positive clinical experience is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute pain subject to condition that clinical trial data needs to be generated in adequately powered study comparing 3 drug FDC with 2-drug combination of Serratiopeptidase/NSAID+ Paracetamol within one year from the date of final decision on marketing of these FDCs .<br><br>Further, Dr Y K Gupta and Dr Nilima Kshirsagar suggested that for serratiopeptidase there needs to be data available substantiating its absorption. This could be in form of documented evidence, and in absence of same, the industry has to conduct a study to prove that orally administered |
| 34 | Diclofenac+ paracetamol+ Tizanidine | Committee observed that there are no published data on safety and efficacy. Further, muscle reluxant Tizanidine is given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Tizanidine + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs. |
| 35 | Dicyclomine+ Diclofenac Sodium+ Paracetamol | This FDC was stated to be indicated as antispasmodic analgesic whenever there is a risk of gastric spasm. Committee opined that a three drugs vs. two drugs Clinical Trial is required to be conducted in a significant number of subjects before considering further. |

| Annexure-A | | |
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| **S.No.** | **Name of FDC** | **Recommendation of Experts** |
| 36 | Dicyclomine+ Ranitidine | Dr. S. K. Acharya, the expert from AIIMS, New Delhi opined that there is no documented evidence in support of safety and efficacy for these combination products. After detailed deliberation, committee recommended that well designed clinical trials in adequate number of patients need to be conducted. Clinical trial protocol should be developed in consultation with the experts. |
| 37 | Domperidone+ Paracetamol | The rationality of the FDC was considered. The FDC of the analgesic and prokinetic /antiemetic cannot be considered rational for general purpose of any kind of pain except migraine. Migraine is a specific pain that is frequently associated with nausea and vomiting and therefore sometime antiemetic is required. It was discussed that combining Domperidone with Analgesic may lead to unnecessary exposure of Domperidone to patients. The committee felt that a clinical trial is required to be carried out in this regard and if the manufacturer has evidence of clinical trial, same may also be considered. |
| 38 | Domperidone+ Paracetamol+ Tramadol | The rationale for the FDC was considered. Tramadol is an opoid analgesic and is combined with Paracetamol in cases of severe to moderate pain. Although, Paracetamol and Tramadol have been used for moderate to severe pain with higher efficacy, evidence for use of the FDC in migraine is lacking.<br>The clinical evidence is lacking regarding the reduction in incidence of nausea/vomiting when the combination is used in migraine. Accordingly, a clinical trial is required to be carried out. Committee therefore felt that evidence needs to be generated to demonstrate:<br><br>1. Superiority of combination of Tramadol + Paracetamol + Domperidone vs Tramadol +Paracetamol on recommended dose in migraine patients.<br>2. Beneficial effect of the Domperidone in the combination in all migraine patients.<br>3. Specific advantages of combining three drugs in this FDC.<br><br>However, if the manufacturer has evidence of clinical trial to support the above points, same may also be considered. |
| 39 | Doxycycline+ Lactobacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 40 | Drotaverine+ Nimesulide | The FDC was discussed in detail. Committee opined that the majority of the conditions of pain may not require antispasmodic. In some visceral pain where there is requirement of anti-spasmodic, an anti-inflammatory may not be required. Further, the combination of Drotaverine + Nimesulide has not been shown to offer any enhanced efficacy. Although there is one study JIMA, 1999, Sept.97(9):398-400 which has shown enhanced efficacy of Diclofenac + Pitofenone fenperivanum.<br>The members opined that above combinations may likely to be misused in larger situations and will increase the probability of side effects of individual drugs. Committee also noted that Nimesulide has been banned because of adverse risk profile in children. In adults, the drug is under focus pharmacovigilance. Therefore the only indication of Dysmennorhea and colic pain were discussed in detail and members opined that sequential need basis treatment is appropriate wherever required. If and when the firm produce a data of increased therapeutic benefit of FDC through literature or by way of generating data, the combination can be reconsidered.<br>All members agreed that this combination is not rational for all pain. Committee also opined that above FDCs can be considered only for one indication i.e. dysmennorhea. However, the data of superior efficacy should be generated. |
| 41 | Drotaverine+ Paracetamol | The FDC was discussed in detail. Committee opined that the majority of the conditions of pain may not require antispasmodic. In some visceral pain where there is requirement of anti-spasmodic, an anti-inflammatory may not be required. Further, the combination of Drotaverine + Nimesulide has not been shown to offer any enhanced efficacy. Although there is one study JIMA, 1999, Sept.97(9):398-400 which has shown enhanced efficacy of Diclofenac + Pitofenone fenperivanum.<br>The members opined that above combinations may likely to be misused in larger situations and will increase the probability of side effects of individual drugs. Committee also noted that Nimesulide has been banned because of adverse risk profile in children. In adults, the drug is under focus pharmacovigilance. Therefore the only indication of Dysmennorhea and colic pain were discussed in detail and members opined that sequential need basis treatment is appropriate wherever required. If and when the firm produce a data of increased therapeutic benefit of FDC through literature or by way of generating data, the combination can be reconsidered.<br>All members agreed that this combination is not rational for all pain. Committee also opined that above FDCs can be considered only for one indication i.e. dysmennorhea. However, the data of superior efficacy should be generated. |

| Annexure-A | | |
|---|---|---|
| S.No. | Name of FDC | Recommendation of Experts |
| 42 | Ibuprofen+ Paracetamol+ Serratiopeptidase | 3 drug combination of Serratiopeptidase + Paracetamol + Aceclofenac / Diclofenac / Ibuprofen / Nimesulide needs to be demonstrated to be superior in efficacy than Serratiopeptidase/NSAID + Paracetamol (2 drug FDC). Since the published data on efficacy of 3 drug FDCs are not available clinical opinion was sought from the clinicians attending the meeting. Although the clinicians especially the practicing Orthopedic surgeons supported the usefulness of serratiopeptidase, it was concluded that documented evidence complementing the positive clinical experience is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute pain subject to condition that clinical trial data needs to be generated in adequately powered study comparing 3 drug FDC with 2-drug combination of Serratiopeptidase/NSAID+ Paracetamol within one year from the date of final decision on marketing of these FDCs .<br><br>Further, Dr Y K Gupta and Dr Nilima Kshirsagar suggested that for serratiopeptidase there needs to be data available substantiating its absorption. This could be in form of documented evidence, and in absence of same, the industry has to conduct a study to prove that orally administered |
| 43 | Lincomycin+ Lactobacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 44 | Nimesulide+ Paracetamol+ Serratiopeptidase | 3 drug combination of Serratiopeptidase + Paracetamol + Aceclofenac / Diclofenac / Ibuprofen / Nimesulide needs to be demonstrated to be superior in efficacy than Serratiopeptidase/NSAID + Paracetamol (2 drug FDC). Since the published data on efficacy of 3 drug FDCs are not available clinical opinion was sought from the clinicians attending the meeting. Although the clinicians especially the practicing Orthopedic surgeons supported the usefulness of serratiopeptidase, it was concluded that documented evidence complementing the positive clinical experience is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute pain subject to condition that clinical trial data needs to be generated in adequately powered study comparing 3 drug FDC with 2-drug combination of Serratiopeptidase/NSAID+ Paracetamol within one year from the date of final decision on marketing of these FDCs .<br><br>Further, Dr Y K Gupta and Dr Nilima Kshirsagar suggested that for serratiopeptidase there needs to be data available substantiating its absorption. This could be in form of documented evidence, and in absence of same, the industry has to conduct a study to prove that orally administered |
| 45 | Ofloxacin+ Lactic acid bacillus | FDC of Antibiotics with Lactobacillus is not irrational however Lactic Acid Bacillus should be not less than 5 billion daily dose for adults. A cautionary note for pregnant/lactation women should be added. Further committee recommended that a PMS data on incidence of prevention of diarrhea and opportunistic infections (clostridium) be generated in 2 years of time. However, published data may also be submitted in this regard. If not, phase IV trial is required to be conducted. |
| 46 | Ondansetron+ Ranitidine | Dr. S. K. Acharya, the expert from AIIMS, New Delhi opined that there is no documented evidence in support of safety and efficacy for these combination products. After detailed deliberation, committee recommended that well designed clinical trials in adequate number of patients need to be conducted. Clinical trial protocol should be developed in consultation with the experts. |
| 47 | Propranolol+ Diazepam | The committee opined that the FDCs may be considered only for acute anxiety disorders. However pharmacokinetics study is required to be carried out to prove that there is no drug-drug interaction between the individual drugs in the formulation before considering it for the said indication. |
| 48 | Tizanidine+ Nimesulide+ Paracetamol | Committee observed that there are no published data on safety and efficacy. Further, muscle reluxant Tizanidine is given for short term use while paracetamol, diclofenac etc. are administered for longer time period in case of arthritis patients. Although clinician opined in favour of the above three drugs FDCs based on their experience and information received from the pharmaceuticals companies, it was concluded that documented evidence in support of clinical safety and efficacy is necessary. After detailed deliberation, committee recommended that these FDCs can be considered only for short term use in acute musculoskeletal pain associated with spasms subject to the condition that statistically powered clinical trials comparing 3 drugs FDC with 2-drug combination of Tizanidine + Paracetamol is required to be conducted within one year from the date of final decision on marketing of these FDCs. |
| 49 | Torsemide+ Spironolactone | The representative from the association informed that it is used as congestive heart failure and liver cirrhosis. The committee opined that the FDC seems to be rational. However, it needs to be justified.<br><br>Torsemide is a better drug than furosemide. Potassium loss is taken care by Spironolactone in this FDC. The committee suggested that PSUR need to be generated with the FDC. |

F. No. 04-146/2007-DC
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(FDC Division)

FDA Bhawan, Kotla road,
New Delhi

Dated: 12 DEC 2018

To

All State/UT Drugs Controllers

Subject:- **Consideration of the directions of Hon'ble Supreme Court of India in the case of 294 FDCs in respect of FDCs which require further generation of data -reg.**

Sir,

The office of Drugs Controller General (India) received complaints from Consumer Associations in year 2007 regarding Fixed Dose Combinations (FDC) not approved by DCG(I) but marketed in the country. As a part of follow up action of complaints, the office of DCG(I) prepared a list of 294 FDCs and directions were issued to all State/UT Drugs Controllers to withdraw these 294 FDCs which were licensed without approval of DCG(I). The manufacturers association, however, got stay from the Hon'ble High Court of Madras on the directions issued in the matter.

The matter was then placed in DTAB in the 56th meeting dated 16.01.2008. A Sub-Committee was constituted by DTAB to examine these FDCs. Accordingly, the Sub-Committee examined these FDCs and submitted its report to the DTAB. DTAB in its meeting held on 16.02.2015 agreed with the recommendations of Sub-Committee of DTAB. The Hon'ble Supreme Court as per its judgement dated 15.12.2017 has accepted the recommendations of DTAB.

As per the recommendations of DTAB, there are 17 FDCs for which data provided by the manufacturer was considered inadequate to prove its rationality, safety & efficacy. List of these FDCs is annexed herewith as **Annexure-A.**

You are requested to direct all concerned manufacturers of the above mentioned 17 FDCs under your jurisdiction to submit the information/data in the prescribed format in hard copy as well as soft copy(i.e. in CD form) as per **Annexure-B latest by 28.02.2019** so that further action can be taken in these FDCs.

It may also be communicated that in case of non-submission of data, this Directorate reserves the right to make its decision on the basis of information available before it in light of the judgement of the Hon'ble Supreme Court.

Yours faithfully,

(Dr. S. Eswara Reddy)
Drugs Controller General (India)

Copy for information and necessary action to:-

1. Web site of CDSCO.
2. CDSCO Zonal and Sub-Zonal offices.
3. All Drugs manufacturer association with the request to publicise it widely amongst their members for submitting the data.

**Annexure A**

| Sr. no. | Name of FDC |
|---|---|
| 1 | Acetyl salicylic acid+Ethoheptazine |
| 2 | Allantoin+Dimethicone+Methylparaben+Propylparaben |
| 3 | Aloe extract+allantocin+Alfa tocoferal acetate+D-panthemol+VitA |
| 4 | Aloe extract+Vit-E+Dimethicone+Glycerine |
| 5 | Aloe vera+Jojoba oil+Vit-E |
| 6 | Aloe vera+Orange oil |
| 7 | Aloe vera+Vit-e acetate |
| 8 | Aloe+tocopherol |
| 9 | Aloevera+Glycerine+PEG 100 stearate+Vit E |
| 10 | Aloevera+Jojoba oil+Wheat germ oil+Tea tree oil |
| 11 | Aloevera+Vit-E+Herbal |
| 12 | Ampicillin+Flucloxacillin Sodium Salt |
| 13 | Ampicillin+Flucloxacillin Sodium Salt+Lactobacillus Acidophilus |
| 14 | Dicyclomine+Paracetamol+Clidinium Bromide |
| 15 | Dicyclomine+Paracetamol+Clidinium bromide+Chlordiazepoxide |
| 16 | Gliclazide+Chromium picolinate |
| 17 | Paracetamol+Lignocaine |

## Annexure B

## Format for submission of information on FDC

(Submit information as hard copy as well as soft copy)

<table>
<tr><th>S. No.</th><th>Item</th><th colspan="2">Response</th></tr>
<tr><td rowspan="5">1.</td><td>(a) Composition of Product: (Details of all strengths/dosage forms)</td><td colspan="2"></td></tr>
<tr><td>(b) Brand name/s, if any:</td><td colspan="2"></td></tr>
<tr><td>(c) Name of the Applicant, specify if<br>i. Manufacturer:<br>ii. Marketer :<br>iii. Petitioner/appellant</td><td colspan="2"></td></tr>
<tr><td rowspan="5">(d) Approving authority with year of approval</td><td>Name of the Authority</td><td>Year of Approval</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
</table>

Signature of the Authorized representative: _____

Name: _____

Designation: _____

Date: _____

Place: _____

Communication (Address, Telephone, Email) Details:

Company Seal:

| S. No. | Item | Response |
|---|---|---|
| 2. | Particulars of the drug: Dosage form, composition of the formulation (including all active ingredients, pharmacological classification) | |
| 3. | Indication(s) | |
| 4. | Provide a copy of Package insert as per Schedule Y of Drugs & Cosmetics Rules. | |
| 5. | State the category (as per Appendix VI) under which FDC approval is claimed | |
| 6. | a) Therapeutic justification / rationale for each ingredient and quantity in the FDC | |
| | b) Therapeutic value claimed or purported to be claimed of the FDC (Postulated advantage/ value of FDC)<br>(Submit a one-page summary with highest level of evidence, supporting the claim of postulated advantage/rationale. The evidence should be enclosed in the form of maximum of five relevant full text articles in peer-reviewed journals/ relevant pages from textbooks)<br>[Tick (√) appropriate option(s)] | |
| | i. Increased efficacy | |
| | ii. Reduced incidence and/or severity of adverse effects | |
| | iii. Dose reduction | |
| | iv. Reduced cost | |
| | v. Booster for another drug | |
| | vi. Improved patient adherence/ Convenience | |
| | vii. Minimization of abuse of other actives | |
| | viii. Simpler logistics of procurement and/ or distribution | |
| | ix. Reduced development of microbial resistance | |
| | x. Any other (please specify) | |

| S. No. | Item | Response |
|---|---|---|
| 7. | Pharmacokinetic/ pharmacodynamics rationality with half-life details of individual ingredients, dosage schedule of individual drugs<br>(Submit a one-page summary with highest level of evidence, supporting the claim of postulated advantage/rationale. The evidence should be enclosed in the form of maximum of five relevant full text articles in peer-reviewed journals/ relevant pages from textbooks) | |
| 8. | Published data regarding safety and efficacy of FDC<br>(Submit a one-page summary with highest level of evidence, supporting the claim of postulated advantage/rationale. The evidence should be enclosed in the form of maximum of five relevant full text articles in peer-reviewed journals/ relevant pages from textbooks) | |
| 9. | Original Safety & Efficacy data if any, regarding the FDC, generated by the applicant<br>(Submit a one-page summary.Also submit the article based on these data, if publishedorone-page abstract of each study if unpublished with CTRI number, if available) | |
| 10. | Regulatory status of the FDC in other countries | |
| 10.1 | Countries where the drug is: | |
| | (a) Marketed | |
| | (b) Approved | |
| | (c) Approved as IND | |
| | (d) withdrawn, if any, with reasons | |
| 10.2 | Restrictionson use, if any, in countries where marketed/approved | |
| 11 | Specimen of labels and cartons | |
| 12 | Any other relevant information | |

**(Note: Individual Form shall be submitted for each FDC and all above information shall be provided for each**